ABERRANT MECHANICAL LOADING IN KNEE OSTEOARTHRITIS: MODEL-BASED ANALYSIS OF GAIT AND STAIR NEGOTIATION

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“A person who never made a mistake never tried anything new.”

Albert Einstein

Contents

List of acronyms

ACR	American College of Rheumatology
AoR	Axis of Rotation
BMI	Body Mass Index
BML	Bone Marrow Lesions
BW	Body Weight
COMAK	Concurrent Optimization of Muscle Activations and Kinematics
CoP	Centre of Pressure
CP	Contact Pressures
DoF	Degree of Freedom
EMG	Electromyography
FAR	Functional Axis of Rotation
f_{RF}	Femoral reference frame
t_{RF}	Tibial reference frame
GRF	Ground Reaction Force
HOOS	Hip Injury and Osteoarthritis Outcome Score
ID	Inverse Dynamics
IK	Inverse Kinematics
KAM	Knee Adduction Moment
KCF	Knee Contact Force
KFM	Knee Flexion Moment
K&L	Kellgren and Lawrence
KOA	Knee Osteoarthritis
KOOS	Knee Injury and Osteoarthritis Outcome Score
KRM	Knee Rotation Moment
LED	Light Emitting Diodes
LKCF	Lateral Knee Contact Force
nwFAR	non-weight-bearing Functional Axis of Rotation
MKCF	Medial Knee Contact Force
MRI	Magnetic Resonance Imaging
OA	Osteoarthritis
RoM	Range of Motion
SARA	Symmetrical Axis of Rotation Approach
SBS	Step-By-Step
SO	Static Optimization

SOS	Step-Over-Step
TEA	TransEpicondylar Axis
TKA	Total Knee Arthroplasty
TKCF	Total Knee Contact Forces
wFAR	weight-bearing Functional Axis of Rotation

Abstract

Four studies were conducted in this PhD aiming to evaluate knee joint loading assessed by calculating knee contact forces (KCF) using a musculoskeletal modeling workflow during common daily-living activities as walking and more demanding tasks, in individuals with varying levels of medial knee osteoarthritis (OA) severities. In **study I**, KCF were calculated and its relations with knee external knee adduction moments (KAM) and/or flexion moments (KFM) assessed during the stance phase of gait. Knee loading was evaluated in individuals with early medial knee OA, classified based on early joint degeneration on MRI and compared to individuals with established medial knee OA and healthy subjects. The effect of using an anatomical *versus* a functional axis of rotation (FAR) on KAM in healthy subjects and patients with knee OA was investigated in **study II**. In addition, this study reports KAM for models with FAR calculated using weight-bearing and non-weight-bearing motion. **Study III** calculates KCF and contact pressures during *gait* and *step-up-and-over* tasks in subjects with early knee OA and those with established knee OA compared to healthy subjects using a multi-body knee model with articular cartilage contact, 14 ligaments, and 6-DoF tibiofemoral and patellofemoral joints. Finally, **study IV** assessed trunk kinematics, KCF and knee contact pressures in individuals with medial knee OA during different stair negotiation strategies: step-over-step (SOS) at controlled speed, and also SOS at self-selected speed and step-by-step (SBS).

This PhD contributed to, firstly, describe the importance of calculating the KCF in both medial and lateral knee compartments to better assess loading changes in individuals with varying levels of medial knee OA severities, especially those with early knee OA, during gait. The medial KCF provided a more sensitive metric to knee joint loading than external KAM or total KCF. Secondly, KAM was shown to be sensitive to the knee axis of rotation, indicating that differences between subject groups might be heavily dependent on the knee axis definition. Finally, different mechanisms used by these patients were identified during gait *versus* step/stair activities when

compared to healthy subjects. Stair negotiation forced the use of compensatory mechanisms in patients with knee OA while gait did not.

Resumo

Quatro estudos foram feitos no âmbito deste doutoramento com o objectivo principal de avaliar as cargas a que a articulação do joelho está sujeita durante actividades do quotidiano, tais como a marcha e a subida/descida de degraus ou escadas, em indivíduos com diferentes graus de desenvolvimento de osteoartrite do compartimento medial do joelho. Este cálculo foi feito com recurso a modelos musculosesqueléticos computacionais e simulações dinâmicas de movimento que permitem estimar as forças de contacto. No **estudo I** foram calculadas as forças de contacto do joelho e relacionadas com os momentos externos de flexão e adução durante a fase de apoio da marcha. As cargas na articulação do joelho foram avaliadas em indivíduos com OA precoce no compartimento medial do joelho, cuja classificação foi baseada na degeneração precoce observada a partir de Ressonância Magnética, mas também em indivíduos em fases já avançadas da doença. O efeito resultante de usar um eixo de rotação anatómico *versus* funcional (ERF) no cálculo do momento de adução da articulação do joelho foi investigado no **estudo II** em pacientes com OA. Além disso, este estudo apresenta os momentos de adução resultantes de duas diferentes definições de eixo de rotação funcional: eixo funcional calculado a partir de movimento sob acção de carga e sem acção de carga. O **estudo III** avaliou as cargas do joelho e pressões de contacto durante a marcha e durante a subida e descida de um degrau, em pacientes que presentam OA precoce e avançada no compartimento medial do joelho comparados a indivíduos saudáveis usando um modelo do joelho mais complexo, que integra um modelo de contacto na superfície articular, 14 ligamentos e 6 graus de liberdade em cada uma das articulações tibiofemoral e patelofemoral. O **estudo IV** avaliou as forças de contacto e as pressões de contacto em pacientes com OA no compartimento medial do joelho durante diferentes estratégias usadas para subir e descer escada: degrau-após-degrau à velocidade em que cada indivíduo se sentia mais confortável; degrau-após-degrau a uma velocidade controlada, mais elevada; e, finalmente, executando a actividade degrau-a-degrau.

Este doutoramento contibuiu, em primeiro lugar, para descrever a importância de calcular separadamente as forças de contacto em ambos os compartimentos do joelho, durante a marcha, para compreender melhor as alterações ocorridas em indivíduos com diferentes níveis de desenvolvimento da osteoartrite, especialmente pacientes com OA precoce. As forças de contacto mediais mostraram ser uma métrica mais sensível na detecção a doença precocemente do que as forças de contacto totais ou os momentos externos. Em segundo lugar, a sensibilidade do cálculo dos momentos de adução face à definição do eixo de rotação do joelho, indicando que as diferenças entre grupos pode estar dependente da definição usada mais do que do avanço da doença. Por último, foram identificados diferentes mecanismos usados pelos pacientes, comparativamente a indivíduos saudáveis, durante a marcha e durante a subida/descida de escadas. Actividades fisicamente mais exigentes forçam os pacientes a usar mecanismos de compensação que não sentem serem necessários durante a marcha.

Chapter 1

General introduction and outline

1.1 Background

1.1.1 Knee Osteoarthritis

Osteoarthritis (OA) is a complex chronic degenerative and multifactorial joint disease that most frequently affects the knee (Lories *et al.*, 2011) and for which there is no effective treatment. According to the World Health Organization, more than 150 million people, corresponding to about 2.5% of the population (Reijman *et al.,* 2007) and about 10% of men and 18% of women aged 60 years or older (Woolf and Pfleger, 2003) suffer from OA worldwide. In almost 30% of these cases, OA leads to moderate to severe disability (Reijman *et al.,* 2007). Symptomatic knee OA, more specifically, affects roughly 12% of the worldwide population above 60 years old (Felson *et al.,* 1998). The prevalence of OA will increase as the population average life expectancy increases, and especially if the incidence of obesity remains over 50% in the 45+ age group (al-Shammari *et al.,* 1994).

In the past, OA was thought to be mainly driven by degeneration of the articular cartilage within the synovial joint. However, over time, it has been proven that not only cartilage, but also the subchondral bone, menisci, ligaments, the synovial fluid, muscles and neural tissues are involved in the complex initiation and progression of the knee OA (Jordan *et al.,* 2011; Blagojevic *et al.,* 2010, Felson *et al.,* 1998; Saris *et al.,* 2009). OA is, therefore, a whole joint disease rather than simply a degenerative cartilage (Figure 1.1). Consequently, patients complain of joint pain, reduced range of joint movement, stiffness, instability, swelling, muscle weakness, and alterations in proprioception (MacKay *et al.,* 2014; Kaufman *et al.,* 2001). These symptoms significantly restrict the individual's physical capacity in activities of daily living, such as getting up from a chair, climbing/descending stairs or simply walking (Losina *et al.*, 2013). This, of course, results in loss of independence, reduced quality of life and ultimately high health-related costs (Bhatia *et al.*, 2013).

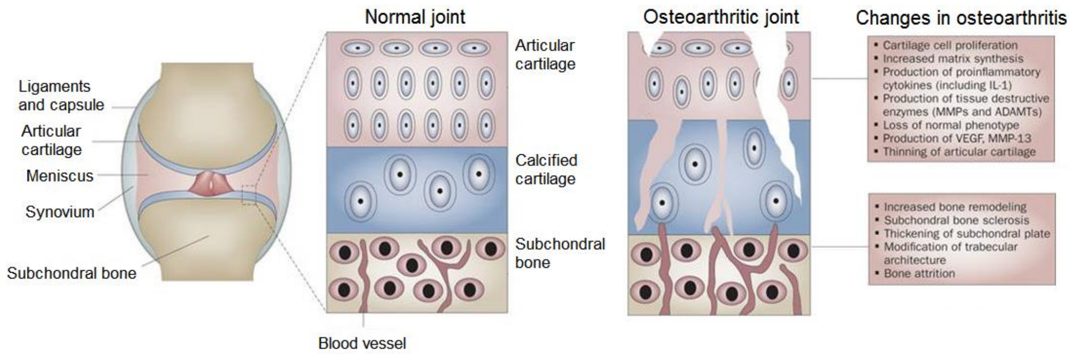

Figure 1.1 - The bone–cartilage unit is at the center of joint function and disease (adapted from Lories and Luyten, 2010) Nat Rev Rheumatol).

Although synthoms in OA are commonly observed across patients, the clinical expression of this disease will be also dependent on other aspects. The individual experience and expression of this disease reflect also important aspects of their live, such as psychological, social, and cultural factors. These aspects will be also reflected as quantitative variations in the biochemical or biomechanical defect of OA. The so-called biopsychosocial model (Engel, 1977) is a model that takes all these factors into account. Therefore, for better understanding of OA, as any other disease, using such a model to look at patients in light of their psicological, social and cultural context may be beneficial. This manuscript, however, approached OA using the biomedical model, more specific by studying biochemical factors observed in medical imaging and self-evaluation of physical condition, and by investigating how these are reflected to biomechanical loading during gait, therefore excluding psychological, environmental or social influences.

1.1.2 Diagnosis in knee OA

Pathogenetically, knee OA is characterized by structural changes, more specifically: loss of cartilage, osteophytes formation, and also subchondral bone sclerosis and cysts that can be radiographically observed in early stages (Luyten *et al.*, 2012) and graded according to the Kellgren and Lawrence (K&L) grading scale (Kellgren JH and Lawrence, 1957). Rather than these structural changes, more recently, new techniques in magnetic resonance imaging (MRI) and arthroscopy have been helpful in visualizing tissue alterations that identify more extended joint involvement and loss of joint homeostasis. These tissue alterations reveal changes in cartilage morphology such as cartilage fibrillation and defects, more diffuse cartilage loss, meniscal damage with tears, degeneration and extrusion of the meniscus, bone marrow lesions (BMLs), subchondral sclerosis and cysts, synovitis or presence of joint fluid. The identification of these tissue alterations allows an earlier diagnosis of knee OA. Early detection of OA is tremendously important, since it allows early interventions aiming to protect the joint integrity before major structural damage occurs. This is important as it is often hypothesized that the ineffectiveness to delay OA may be mainly caused by a late intervention, when structural deterioration is already advanced. Therefore, there is currently a higher clinical interest in identifying OA in more early stages of the disease (Luyten *et al.*, 2012).

1.1.3 Biomechanics and knee loading

The causes of OA are complex and involve interrelated biological (Lohmander *et al.*, 1999; Maniwa *et al.*, 2001; Otterness *et al.*, 2001), mechanical (Beaupre *et al.*, 2000; Carter *et al.*, 1998; Grodzinsky *et al.*, 2000; Mow *et al.*, 2002), and structural (Eckstein *et al.*, 2002; Koff *et al.*, 2003; Mow *et al.*, 1992; Peterfy *et al.*, 1994) pathways (Figure 1.2). Risk factors such as older age, female gender, obesity (particularly in knee OA), previous joint injury or trauma, specific occupations with repetitive tasks or overuse, genetic predisposition, bone deformities, malalignment, and muscle weakness are known to contribute to the process of OA initiation (Luyten *et al.*, 2012).

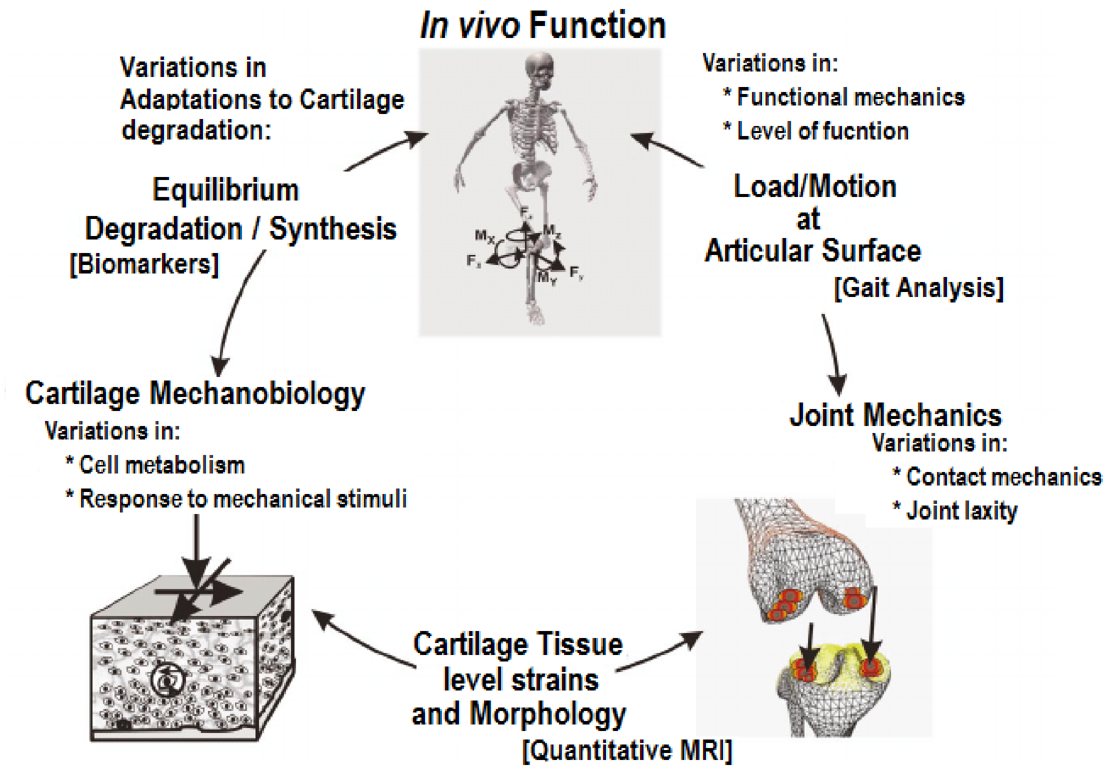

Figure 1.2 - The interrelationship of the different pathways involved in knee OA. In-vivo response of articular cartilage to its physical environment requires an integrated view of the problem that considers functional, anatomical, and biological interactions (Andriacchi et al., 2004).

The mechanism behind the biomechanical factors in the initiation of knee OA has been described by Radin *et al.* (1986), who explains that the integrity of articular cartilage not only depends on stresses induced by joint loading placed upon the cartilage but also on reactive stresses generated underneath the cartilage. Indeed, functional activities such as gait and stair climbing enforce higher mechanical loads to the medial than to the lateral compartment given the medially directed ground reaction force (GRF) during these activities (Hurwitz *et al.*, 2002; Lewek *et al.*, 2004). In addition, in the presence of subchondral bone remodeling in response to mechanical overload, the efficiency of cartilage as a shock absorber decreases and local cartilage lesions can occur, especially in the ageing cartilage (Radin *et al.*, 1986). Therefore, aberrant knee joint loading on the medial knee compartment has indeed been identified as a potential factor affecting the progression of knee OA (Sharma *et al.*, 2001; Brouwer *et al.*, 2007) and might be associated with the higher incidence of OA in the medial (Wise *et al.*, 2012) than the lateral knee compartment. Furthermore, as mentioned above, OA affects the entire joint. Consequently, variations in the soft tissue properties and structure (Ateshian *et al.*, 1991; Cicuttini *et al.*, 2002; Cohen *et al.*, 1999) also influence the congruency and laxity of the joint, and produce substantial variations in contact stresses and locations which in turn further impact the cartilage mechanical environment. As cartilage adapts to mechanical stimuli (Smith *et al.*, 1995; Smith *et al.*, 2000) and its normal tissue function depends on the maintenance of these stimuli (Carter *et al.*, 1998), variations in the weight-bearing regions during walking have been associated with regional variations in cartilage thickness (Koo *et al.*, 2003; Van Rossom *et al.*, 2017). Thicker cartilage has been associated with higher cartilage loading during walking, and increased proteoglycan and collagen concentration has been associated with higher pressures and compressive forces (Van Rossom *et al.*, 2017). In response to this plethora of pathological changes in the knee joint that causes physical limitations, patients adopt altered locomotor patterns. Consequently, adaptations in locomotion might shift the normal load bearing contact to cartilage regions that are not accustomed to high loads leading to a faster progression of the disease. Therefore, it is not only important to evaluate the presence of mechanical joint overloading in patients suffering from knee OA but also the locations of the loaded regions on the articular surface, as this might be an important factor influencing OA initiation and/or progression.

1.1.4 Gait Analysis in knee OA

Gait analysis has been largely used as a clinical tool to evaluate and discriminate patients with knee OA of varying severity. Clinical gait analysis is performed to provide a diagnosis; to assess the severity, extent or nature of a disease or injury; to monitor progress in the presence of intervention, such as, therapy (Ramsey et al., 2007; Ramsey et al., 2009; Barrios et al., 2013) or surgery (Georgoulis et al., 2003) or in the absence of intervention; and, ultimately, to predict the outcomes of a certain intervention or the absence of intervention (Baker, 2006; Brand and Crowninshield, 1981). In patients with medial knee OA, excessive medial loading during daily-living activities, especially during walking, has been estimated indirectly using external knee adduction moment (KAM). KAM is largely determined by the ground reaction force vector and its lever arm to the knee joint centre. More recently, a few studies (Richards *et al.*, 2010; D'Lima *et al.*, 2012; Kumar *et al.*, 2013) have reported knee contact forces, that are calculated using more complex musculoskeletal knee models taking muscle and ligament forces into account. Those studies have mostly been performed in patients with severe knee OA.

Knee Adduction Moment in knee OA

To assess changes in kinematics and kinetics of weight-bearing joints in degenerative disorders such as knee OA, gait analysis has been widely used. Medial compartment loading assessed by KAM has been widely reported in the literature during functional activities of patients with medial knee OA. Increased KAM has been associated with more pronounced clinical symptoms and OA severity as assessed by radiography (Baliunas *et al.*, 2002; Andriacchi *et al.*, 1994; Fregly *et al.*, 2007; Mundermann *et al.*, 2008a; Hurwitz *et al.*, 2000, Guo *et al.*, 2007; Miyazaki *et al.*, 2002; Lewek *et al.*, 2004). While the role of mechanical loading assessed by KAM in patients with moderate and severe knee OA has been documented, mechanical loading has not been deeply explored in individuals with only early signs of joint degeneration. Three recent articles have shown that there is no evidence of increased KAM in patients with early knee OA compared to healthy controls during walking (Foroughi *et al.*, 2009; Baert *et al.*, 2013; Duffell *et al.*, 2014). However, the contribution of muscles and ligaments to joint loading is not taken into account when the knee joint loading is assessed by KAM only (Richard *et al.*, 2010; Kumar *et al.*, 2013; Meyer *et al.*, 2013). Consequently, these studies potentially fail to describe the more subtle changes in loading characteristics in early OA patients where structural degeneration is less pronounced. Furthermore, medial compartment knee loading was found to be related to a combination of both KAM and knee flexion moment (KFM) during walking (Kumar *et al.*, 2013), therefore questioning the role of KAM as sole indicator of medial compartment knee loading.

In gait analysis, joint angles are calculated based on the body segments' 3D positions and orientation measured from markers placed on the subject's skin. By performing an inverse dynamics approach on a multi-body skeletal model that describes the body segment's inertial parameters, the kinematic information in combination with external reaction forces, allows the calculation of the joint moments acting about the knee. Therefore, the accuracy of KAM depends on the accuracy of the calculated joint angles, which in turn depends on the accuracy of the definition of the knee axis of rotation (AoR) in the model. A misorientation of the AoR not only affects the joint angle calculation but also knee joint moments, introducing uncertainty on one of the major outcome measures on joint loading in OA patients. The AoR can be estimated based on skin markers placed at the prominences of the medial and lateral knee epicondyles, the so-called transepicondylar axis (TEA) and this approach is commonly used in many gait studies on knee loading in OA (Newell *et al.*, 2008; Ogaya *et al.*, 2014; Levinger *et al.*, 2013; Thorp *et al.*, 2007; Thorp *et al.*, 2006; Astephen *et al.*, 2008; Landry *et al.*, 2007). However, this method introduces the risk of palpation errors when manually positioning the markers. Minor changes in marker placement modify the orientation of the knee joint axis and thereafter lead to significant errors overestimating abduction/adduction angles in the presence of knee flexion, a phenomenon called crosstalk effect (Baudet *et al.*, 2014; Marin *et al.*, 2003). Functional approaches to determine the axis of rotation do not depend on assessing anatomical landmarks (Colle *et al.*, 2012). The functional axis of rotation (FAR) represents the average orientation and location of the instantaneous AoRs throughout a motion (Van Campen *et al.*, 2011) and, therefore, use of a FAR reduces the crosstalk effect in healthy subjects (Schache *et al.*, 2006; Passmore *et al.*, 2016). By affecting the calculation of joint kinematics, the knee AoR definition will also affect the KAM calculationbut to date there is no previous study that quantifiedthe effect of the AoR on the computed KAM. In addition, it is unknown whether the influence of the AoR on the KAM is different between healthy subjects and subjects with knee OA. There are no studies that have evaluated the effect of using a FAR on the KAM during gait in OA patients with different degrees of structural involvement and, therefore, the effects of AoR definition in knee OA are still unknown. In addition, it is still unclear whether FAR should be calculated based on weight-bearing or non-weight-bearing motion. This is highly relevant as passive knee joint laxity (Lewek *et al.*, 2004) and lack of dynamic knee stability (Lewek *et al.*, 2004, Fitzgerald *et al.*, 2004) are present in patients with knee OA and this might have an important effect on the calculated AoR and consequently the calculated KAM.

Knee Contact Forces

Knee contact forces can be directly measured *in vivo* in patients who received instrumented total knee arthroplasty (TKA) (Heinlein *et al.*, 2009; Kutzner2010, Taylor *et al.*, 1998; D'Lima *et al.*, 2005; D'Lima *et al.,* 2006; D'Lima *et al.*, 2007; Mundermann *et al.*, 2008b). However, it is challenging to infer articular loading for subjects with and without knee OA from these measurements because the procedure involves the articular surface replacement, changing the bone structure, and the re-alignment of the mechanical knee axis (Benedetti *et al.*, 2003, Venema *et al.*, 2012). Furthermore, individuals having TKA typically experience a decrease in pain and instability after 3-12 months following surgery, which may reduce muscle co-contraction and, ultimately, alter knee joint loads (Yoshida *et al.*, 2008). Using instrumented total knee prosthesis, peak KCF ranging between 1.9 and 3.5 times body weight (BW) have been found for walking at self-selected speed (Mundermann *et al.*, 2008b; Zhao et al., 2007; Zhao et al., 2007; Kim et al., 2009). Higher KCF, about 4.5BW, have been reported in healthy subjects when assessed by computational approaches (Richard *et al.*, 2010) that might be explained by the biomechanical changes resulting from TKA, as mentioned above. Although it is challenging to infer articular loading for with and without knee OA from instrumented TKA, *in vivo* measurements of the tibial compressive loads are essential to validate computational models (Mundermann *et al.*, 2008b; Varadarajan *et al.*, 2008; D'Lima *et al.*, 2008; Zhao et al., 2007a; Zhao *et al.*, 2007b; Kim *et al.*, 2009; Richard *et al.*, 2010).

Alternatively to direct measurement of KCF, musculoskeletal modeling in combination with simulations of motions might be used to calculate KCF. Different from *in vivo* measurements, computational approaches are non-invasive and can be applied to a larger number of subjects. Therefore, computation of KCF has received much attention (Richards *et al.*, 2010; D'Lima *et al.*, 2012; Kumar *et al.*, 2013). KCF not only account for the external forces but also account for muscle and ligament forces. KCF can be computed using OpenSim's Joint Reaction analyses (Steele *et al.*, 2012) as performed in study I. In this approach, the total knee contact forces and moments are computed from the kinematics and inertial properties of the tibia body (associated with the generalized coordinate), muscle and ligament (when ligaments are included in the model) forces, and external loads based on a musculoskeletal model. These contact forces and moments are the internal forces and moments carried by the joint structure that in combination with muscle forces and ligament forces balance the inverse dynamics external forces and moments. The resultant knee forces (knee contact forces, muscle forces, ligament forces and external forces) are calculated based on the dynamic equilibrium, in which the sum of all the forces acting on a body is equal to the product of the body mass and the linear acceleration (by the Newton's second law). The resultant knee moments, the sum of all the moments acting (internal and external) about the joint is equal to the time rate of change of the angular momentum (by the Newton-Euler equations).

To be able to estimate KCF, muscle forces have to be calculated first. The major problem for the estimation of muscle forces acting around musculoskeletal joints is the problem of redundant muscles. This redundancy results from the higher number of muscles compared to the degrees of freedom of the joint. As a result, there is no unique solutions for the muscle force distribution and hence for KCF. Optimization methods in a static or dynamic configuration have commonly been used to resolve this redundancy by assuming the human movement is produced by optimizing some performance criterion (Pedotti *et al.,* 1978; Anderson *et al.*, 2001; De Groote *et al.*, 2016). Although static optimization neglects muscle activation and contraction dynamics, which are accounted for by dynamic approaches, static optimization results in similar muscle force solutions as dynamic optimization for gait (Anderson *et al.*, 2001). Briefly, static optimization determines the set of muscle forces produce net joint moments while minimizing a cost function based on a certain performance criterion at a discrete time within certain muscle force limits (more in Workflow 1 from Methodology). Previous research (Challis, 1997) has shown that minimizing effort, by minimizing the sum of squared muscle activations, yields muscle activation patterns similar to those observed experimentally and this performance criterion is therefore largely used (Kim *et al.*, 2009; Anderson *et al.*, 2001).

A more recent approach developed by Lenhart et al. (2015), uses an enhanced static optimization technique, the concurrent optimization of muscle activations and kinematics (COMAK) algorithm (Lenhart et al. 2015; Smith *et al.*, 2016) to simultaneously solve for ligament forces, muscle forces, and contact forces in the medial and lateral compartment of the knee joint. COMAK estimates secondary knee kinematics, muscle and ligament forces, and contact pressures based on minimizing a certain cost function while satisfying dynamic equations of motion. This cost function is defined as the weighted sum of squared muscle activations and the net cartilage contact elastic energy. The contact pressures are derived from an elastic foundation model (based on the theory developed by Bei and Fregly, 2004) implemented in the articular cartilage of the knee. This approach was used in study III and IV and it is described in the Workflow 1 from Methodology.

The computational approaches have been also used to assess the knee contact forces in patients with knee OA during level walking (Richard *et al.*, 2010; Kumar *et al.*, 2013). Richards *et al.* (Richards *et al.*, 2010) did not find significant differences in the first peak KCF between healthy subjects and those with varying degrees of OA (all groups presented peak KCF between 4-4.5BW). However, the severe OA group showed a very different KCF pattern compared to healthy subjects, and both OA groups presented reduced second peak KCF. Kumar *et al.* (2013), on the other hand, found increased first peak medial KCF in established OA subjects (2.57 BW) with radiographic signs of joint structural changes (K&L ≥ 2) compared to healthy subjects (2.37 BW) but not in terms of total KCF (3.67 BW and 3.50 BW, respectively, healthy and OA subjects). The average compartmental KCF for a population with severe medial OA throughout the stance phase of gait is presented in Figure 1.3. While compartmental KCF has been reported by Kumar *et al.* (2013) for patients with severe knee OA, there is still a lack of information regarding patients in the early stages of OA both in terms of total KCF and, more importantly, contact forces on the medial compartment of the knee joint.

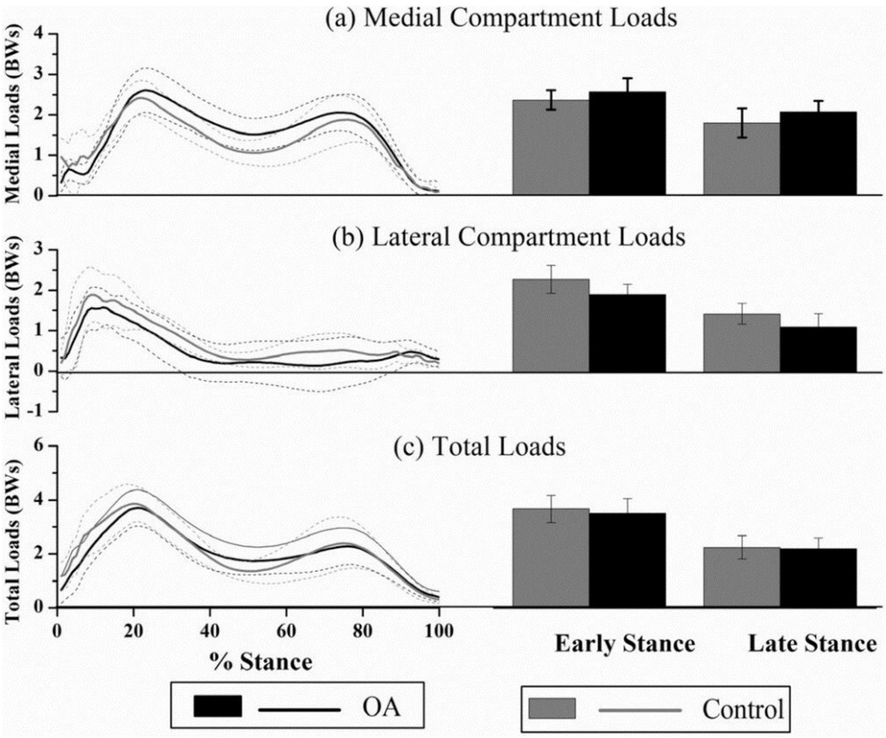

Figure 1.3 - Medial condylar load (a), lateral condylar load (b) and total load (c) for OA (black) and control (gray) subjects over the whole stance phase normalized to body weight (BW) (left panel) and the loading at first and second peak KAM (right panel). Error bars indicate 95% confidence intervals (Kumar et al., 2013).

Stair negotiation in knee OA

Most studies in the literature have focused on knee loading in terms of KAM during walking as biomarkers for OA onset and progression. However, it is during weight-bearing activities as climbing or descending stairs (Hensor *et al.*, 2015) that subjects with knee OA often present the first pain complaints, since these taks are biomechanically more challenging (Nadeau *et al.,* 2003), demand higher ranges of motion (RoMs) in the lower extremity and larger knee moments (Kaufman *et al.*, 2001; Andriacchi *et al.*, 1980; McFadyen and Winter, 1998) and, consequently demand increased quadriceps forces. Furthermore, stair ascent is one of the most highly recommended tests to assess physical function (Dobson *et al.*, 2013; Bennell *et al.*, 2011), including by the Osteoarthritis Research Society International (OARSI) (Dobson *et al.*, 2013). Only a few studies have reported joint moments (Hensor *et al.*, 2015; Guo *et al.*, 2007; Asay *et al.*, 2001; Kaufman *et al.*, 2001; Igawa *et al.*, 2014) and muscle activations (Liikavaino *et al.*, 2010) during stair negotiation in patients with advanced stages of knee OA. Previous literature has shown lower external flexion moments (Hensor *et al.*, 2015, Igawa *et al.*, 2014; Kaufman *et al.*, 2001), some non-conclusive findings in terms of KAM (Kaufman *et al.*, 2001; Linley *et al.*, 2010), and altered muscle activation pattern during stair ascent and descent (Liikavainio *et al.*, 2010) in patients having severe knee OA. Higher trunk flexion angles (Asay *et al.*, 2009; Andriacchi *et al.*, 1985) and hip flexion moment (Asay *et al.*, 2009; Hicks-Little *et al.*, 2011) have also been observed in patients with severe knee OA when compared to healthy subjects while ascending stairs (Asay *et al.*, 2009). These alterations observed in patient with knee OA have been associated with a loss of quadriceps function (Hurley *et al.*, 1998; Slemenda *et al.*, 1997) as these muscles provide the extensor moments required to accelerate the upward propulsive phase during the first part of stair ascent and to decelerate the lowering of the body during stair descent (Lu *et al.*, 2006). To date only kinematics and kinetics (Kaufman *et al.*, 2001; Asay *et al.*, 2009; Lessi *et al.*, 2012), and muscle activation pattern (Liikavainio *et al.*, 2010) have been explored for stair negotiation and step-up (Pozzi *et al.*, 2015), therefore, it is still unknown how the observed alterations in movement patterns affect the medial compartment KCF.

Generally, healthy and young subjects use a traditional step-over-step (SOS) motion pattern, i.e. alternating feet per step, during stair negotiation. On the other hand, patients with knee OA are frequently forced to adjust their stair motion pattern due to knee pain, reduced range of joint motion, muscle weakness, stiffness and instability complaints (Bhatia *et al.*, 2013; Likivainio *et al.*, 2008). Therefore, they often adopt alternative walking patterns, such as increased handrail use, sideways motion, or a step-by-step (SBS) pattern (placing both feet on the same step before ascending or descending) that deviates from the traditional SOS walking pattern (Shiomi *et al.*, 1994; Startzell *et al.*, 2000). On top, they often significantly reduce gait speed to decrease the demands of the task through reducing joint moments (Kaufman *et al.*, 2001; Hicks-Little *et al.*, 2012). However, it has been shown that in healthy subjects, the SBS strategy requires higher energy costs, shows lower efficiency, and increases the risk of falling than SOS during stair ascent (Shiomi *et al.*, 1994). On the other hand, during stair descent, significantly reduced KFM were reported in healthy subjects while performing SBS instead of SOS (Reid *et al.*, 2007), but without coinciding changes in frontal plane moments during either stair ascent or descent. Therefore, a better insight into how these adaptations in stair negotiation affect knee loading and whether they have a positive or negative impact on compartmental KCF and the contact pressure distribution is extremely relevant to assess the comparison with the traditional motion patterns.

1.2 Objective

1.2.1 General Objective

This PhD aims to evaluate knee joint loading in patients with medial knee OA assessed by calculating the KCF during common daily-living activities such as walking and more demanding tasks, such as step-up-and-over and stair climbing and descent. The first studies of the thesis describe mechanical knee loading assessed by external moments and contact forces in patients with varying severities of medial knee OA, with a special focus on those at early stages of the disease, for which diagnosis combines self-reported knee pain with structural changes only detected on MRI (Luyten *et al.*, 2012). Total KCF was calculated during walking and correlated with KAM in patients with early OA as well as with established OA in the medial compartment of the knee, and compared to healthy subjects (**Study I**). Thereafter, the effect of the axis of rotation on the calculation of the KAM was assessed for the same groups of patients (**Study II**). Medial and lateral knee contact forces were then calculated by using a more robust knee model which allows the estimation of the cartilage surface contact pressures during walking and step-up-and-over for the same groups of patients (**Study III**). Finally, the biomechanical strategy used by patients with medial knee OA in more advanced stages during stair negotiation was assessed by estimating the trunk kinematics, knee kinetics, KCF and contact pressures on the tibia plateau under common and alternative stair motion patterns (**Study IV**).

1.3.2 Specific objectives and hypotheses

Objective I – Elaborated in Chapter 2

<u>Knee contact forces are not altered in early knee osteoarthritis</u>

Firstly, this study evaluates whether knee loading during walking, as assessed by KCF, is different in subjects with early medial knee OA compared to healthy subjects and those with established medial knee OA. Secondly, it assesses the contribution of altered frontal and sagittal plane moments to the observed changes in KCF for those subjects at different stages of the disease process. To this end, a standard generic musculoskeletal model (Delp *et al.*, 1990) from OpenSim 3.0 software was used. The knee joint model was then extended with one degree of freedom (DoF) in the frontal plane to estimate knee moments and contact forces in patients with early medial knee OA and with established medial knee OA.

Hypothesis I

Early signs of structural degeneration as present in early OA subjects, lead to increased knee loading compared to healthy subjects but to a lesser extent than in established OA subjects.

Hypothesis II

In early OA patients, presenting limited structural degeneration, frontal plane moments contribute less to the KCF than in patients with established OA.

Objective II – Elaborated in Chapter 3

<u>Differences in knee adduction moment between healthy subjects and patients with osteoarthritis depend on the knee axis definition</u>

This study evaluates the effect of different methods to describe the AoR in the knee joint on the calculated external sagittal (KFM) and frontal (KAM) plane joint moments, often used as biomarkers for OA progression in subjects with different levels of OA involvement (early vs established OA). Functional axes were calculated using three different algorithms with different motions as inputs (walking, step-up-and-over, sit-to-stand-to-sit and dynamic motion comparing weight to non-weight-bearing conditions) and implemented in the generic musculoskeletal model (OpenSim 3.0) to estimate knee moments and these moments were then compared to moments estimated by the generic knee model which includes a transepicondylar AoR.

Hypothesis III

The use of a transepicondylar axis *versus* a functional axis of rotation influence the differences in knee adduction moment between different groups of subjects with knee OA of varying severity.

Hypothesis IV

Knee adduction moment calculated using a functional axis of rotation during weight-bearing motion is significantly different from that calculated using FAR during non-weight-bearing motion due to the presence of structural changes and unstable knee joints in patients with established OA.

Objective III – Elaborated in Chapter 4

Medial knee loading is altered in subjects with early OA during gait but not during step-up-and-over task.

More demanding functional activities such as step-up-and-over impose higher knee joint loading compared to walking. Firstly, this study evaluates the magnitude of knee joint loading (assessed through computed KCF) during gait in patients with early knee OA, and with established knee OA compared to healthy subjects, as well as the maximum contact pressures and their respective locations. To do so, a multi-body knee model (Lenhart *et al.*, 2015) with articular cartilage contact, 14 ligaments, 6-DoF-tibiofemoral and patellofemoral joints and an elastic contact model allowing contact pressures calculation was used. Secondly, this study evaluates whether higher demanding activities as step-up-and-over task serve as more sensitive tasks to discriminate between controls and early OA subjects. Therefore, medial and lateral knee contact forces as well as contact pressure were calculated in early and established OA subjects during walking and step-up-and-over tasks.

Hypothesis V

Knee contact forces and contact pressure distributions are more sensitive than knee joint moments in detecting early changes in knee joint loading in early OA subjects, prior to the onset of structural degeneration.

Hypothesis VI

Higher demanding activities may cause larger alterations in the medial compartment loading, present prior to alterations during gait and, therefore, may be able to discriminate patients with early knee OA from healthy subjects.

Objective IV – Elaborated in Chapter 5

Patients with medial knee osteoarthritis reduce medial knee contact forces by altering trunk kinematics, progression speed, and stepping strategy during stair ascent and descent

This study quantifies knee joint loading during stair negotiation and evaluates the unloading effect of different stair climbing/descending strategies. Firstly, this study evaluates knee joint loading in terms of medial and lateral KCF and contact pressures during stair ascent and descent in patients with medial knee OA compared to healthy subjects while performing SOS strategy at controlled speed. Frequently, patients with knee OA spontaneously adjust their stair walking pattern due to the knee pain, reduced range of joint motion, muscle weakness, stiffness and instability complaint (Bhatia *et al.*, 2013; Likivainio *et al.*, 2008) and, therefore, they often adopt alternate walking strategies. As such, this study, also evaluates knee joint loading resulting from different strategies, more specific SBS patterns as well as the effect of reduced speed (controlled speed *vs* self-selected speed) during stair ascent and descent.

Hypothesis VII

Individuals with medial knee OA present lower knee loading than healthy subjects during stair negotiation trying to avoid pain.

Hypothesis VIII

By reducing the stair walking speed or by using SBS instead of SOS, patients reduce the KCF and redistribute the knee loading to avoid the overloading on the involved compartment.

1.3 Methodology

For study I, II and III, data collection was conducted in Leuven, whereas for study IV, data collection was conducted in Manchester during the mobility period as a part of this PhD project.

The specific data collected for each study is presented in Table 1.1.

Table 1. 1 – Overview of the data collected for each study.

	No. participants	Measurements	No. trials per subject
Study I	20 Control 16 Early medial knee OA 23 Established medial knee OA	3D marker trajectories GRF EMG MRI	12 gait
Study II	20 Control 16 Early medial knee OA 23 Established medial knee OA	3D marker trajectories GRF EMG MRI	12 gait 6 step-up-and-over 6 sit-to-stand-to sit 6 dynamic motion
Study III	19 Control 18 Early medial knee OA 16 Established medial knee OA	3D marker trajectories GRF EMG MRI	12 gait 6 step-up & step-down
Study IV	8 Control (16 limbs) 5 Medial knee OA (10 limbs)	3D marker trajectories GRF EMG; MRI	6 stair ascent (SOS SS) 6 stair descent (SOS SS) 6 stair ascent (SOS CS) 6 stair descent (SOS CS) 12 stair ascent (SBS) 12 stair descent (SBS)

SOS SS and SOS CS correspond, respectively, to the step-over-step at self-selected speed and at controlled speed and SBS to step-by-step. GRF, EMG and MRI correspond, respectively, to ground reaction forces; electromyography; and magnetic resonance imaging.

An overview of the different groups of participants and protocols used in the studies is presented in Table 1.2.

Table 1. 2 – Overview of the protocols used for each study.

			Study I	Study II	Study III	Study IV
Participants		**Group 1**	X	X		
		Group 2			X	
		Group 3				X
Data Collection Protocols	**Motion Analysis**	**Protocol 1**	X	X	X	
		Protocol 2				X
	Medical Imaging	**Protocol 3**	X	X	X	
		Protocol 4				X
Musculoskeletal Modeling		**Workflow 1**	X	X		
		Workflow 2			X	X

1.3.1 Participants

Group 1

Fifty-nine participants (all women, mean age of 65±7.3 years) were recruited in Leuven (Table 1.3) and were divided into three groups: control subjects (*n*=20), early medial knee OA (*n*=16), and established medial knee OA (*n*=23) patients. All procedures were approved by the local ethical committee of Biomedical Science, KU Leuven, Belgium (Ethical Approval=S50534).

Early medial knee OA was diagnosed based on novel classification criteria of Luyten *et al.* (2012), including fulfillment of three criteria, namely knee pain, assessed through the Knee Injury and Osteoarthritis Outcome Score (KOOS) (Dutch version, De Groot *et al.*, 2008); a K&L grade 0, 1 or 2^{-} (osteophytes only); and structural changes observed on MRI.

Established medial knee OA was diagnosed based on slight adaptation of the American College of Rheumatology (ACR) classification criteria (Altman *et al.*, 1986), including knee pain, stiffness less than 30 min and crepitus, together with structural changes defined as presence of minimum grade 2^{+} (osteophytes and joint space narrowing) on K&L scale for at least the medial compartment on radiography.

A control group was also analyzed, which included asymptomatic healthy subjects with no history of knee OA or other pathology involving any lower extremity joints, and with a radiological score of 0 or 1 according to K&L score.

Subjects were excluded from either group if they had musculoskeletal disorders other than knee OA in both lower limbs in the last 6 months, previous surgery of lower extremities and/or low back, neurological disorders, chronic intake of corticosteroids or contra-indications for MRI.

For healthy subjects, both legs were analyzed. For symptomatic patients with unilateral knee OA, only data of the affected knee were analyzed. For those with bilateral knee OA, both legs were analyzed except when the less involved side presented with a K&L score ≤ 2 for the established OA group.

Table 1. 3 – Participants' characteristics from study 1 and 2: control (C0), early OA (EA) and established OA (ES).

	Control	**Early OA**	**Established OA**	***p***	***p* (C0-EA)**	***p* (C0-ES)**	***p* (EA-ES)**
No. of subjects	20	16	23				
Age, *years*	64.6±8.7	64.9±6.0	65.6±7.2	0.910	0.999	0.965	0.989
Body mass, *kg*	65.0±8.0	70.5±14.0	73.2±12.8	0.079	0.417	0.076	0.860
Knee Alignment, ^{0}	-.03±2.15	0.37±3.31	2.77±4.30	**0.020***	0.965	**0.022***	0.067
Gait speed, m/s	1.23±0.20	1.29±0.19	1.21±0.14	0.338	0.659	0.963	0.373

Values are the mean ± Standard Deviation (SD). ANOVA with Gabriel *post hoc* test. Significant difference $p < 0.05$ are indicated with *.

Group 2

The same cohort as study 1 and 2 was initially used for study 3. However, due to convergence problems in the optimization, the participant number dropped to fifty-three in total (all women, mean age of 64.8±7.5 years). Number of subjects included for each task and subjects' characteristics are presented in more detail in Table 1.4. Subjects were again separated into three groups: asymptomatic healthy subjects (*n* = 19) as control; patients with symptomatic early medial knee OA based on the classification criteria of Luyten et al. (2012) (*n* = 18) described above, and patients with symptomatic established medial knee OA based on the ACR (Altman *et al.*, 1986) classification criteria (*n* = 16). All procedures were approved by the local ethical committee of Biomedical Science, KU Leuven, Belgium (Ethical Approval=S50534).

Table 1. 4 - Participants' characteristics from study 3: control (C0), early OA (EA) and established OA (ES).

	Task	Control	Early OA	Established OA	*P*	*p* (C0-EA)	*p* (C0-ES)	*p* (EA-ES)
No. of subjects	***Gait***	17	14	16	-	-	-	-
	Step	19	18	16	-	-	-	-
Age, *years*	***Gait***	64.2±9.0	63.3±7.7	67.2±6.7	0.362	0.985	0.619	0.449
	Step	64.3±8.5	63.3±7.0	67.2±6.7	0.305	0.965	0.598	0.351
Body mass, *kg*	***Gait***	64.0±7.9	69.7±16.6	73.3±11.9	0.103	0.494	0.102	0.809
	Step	64.6±7.7	70.0±15.5	73.3±12.0	0.103	0.440	0.109	0.813
Knee Alignment, ⁰	***Gait***	0.50±2.3	1.46±3.4	3.66±3.5	**0.014**	0.701	**0.010**	0.164
	Step	0.45±2.5	1.14±3.2	4.03±3.5	**0.004**	0.831	**0.003**	**0.034**
Speed, *m/s*	***Gait***	1.21±0.2	1.26±0.2	1.20±0.2	0.426	0.623	0.992	0.524
	Step	0.53±0.1	0.55±0.1	0.57±0.1	0.311	0.663	0.371	0.966

Values are the mean ± Standard Deviation (SD). ANOVA with Gabriel *post hoc* test. Significant difference $p < 0.05$ are indicated in bold.

Group 3

In total, eighteen participants (Table 1.5) were recruited in Manchester. Subjects performed MRIs and completed the Hip (HOOS, Nilsdotter *et al.*, 2003) and Knee (KOOS, Roos *et al.*, 2003) disability and Osteoarthritis

Outcome Score questionnaires to assess functionality and pain of hip and knee, respectively. From ten participants recruited on a volunteer basis from the university context, who were asymptomatic and had no history of knee OA or in any other lower extremity joint, eight healthy participants (completing a total of 16 limbs) were selected. Control participants were excluded if they presented any knee OA evidence observed in the MRI scans. From the initial eight symptomatic knee OA participants recruited via a volunteer database diagnosed with knee OA during clinical practice, five patients with clear bilateral OA at the medial knee compartment (completing a total of 10 limbs) were derived. Participants were excluded if they presented clear lateral knee OA; presented clear patellofemoral knee OA; or had previous surgery of lower extremities. All procedures were approved by the Research Ethics committee for Science & Engineering at the Metropolitan Manchester University (Ethical Approval=SE141502). All participants signed the written informed consent form before the study began.

Patients were classified as having mild (1) moderate (2) and severe (3) knee OA based on pain complaints and three parameters observed on the MRI: cartilage defect; BML; and presence of osteophytes. Cartilage was scored for partial and full thickness loss as a % of the surface area in which: 0 when none; 1 when < 15% of cartilage loss; 2 when 15-75% of cartilage loss; 3 when >75% of cartilage loss in a region (medial, lateral or patellofemoral). BML size was scored as follows: 0 when none; 1 when BML size <1 cm; 2 BML when size >1 cm; 3 when multiple BML. Presence of osteophytes was scored based on their size as follow: 0 when no osteophytes; 1 when size < 5mm; 2 when size < 1cm; 3 when > 1cm. Patients were classified as moderate to severe on the medial compartment. Four patients of the cohort also performed an X-ray at the clinical practice one year before the data collection and the K&L scores varied between 2 and 3.

All included patients presented bilateral medial knee OA and, therefore, both limbs were analyzed completing a total of 10 limbs. For healthy subjects, both legs were analyzed making a total of 16 limbs.

Table 1. 5 - Participants' characteristics from study 4.

	Task	Control	Medial OA	*p* (Control *vs* Medial OA)
No. of subjects		8	5	-
No. of limbs		16	10	-
Age, *years*		51.0±13.4	52.8±11.0	0.806
Body mass, *kg*		74.1±13.7	83.8±14.8	0.255
Height, *m*		1.66±0.10	1.70±0.11	0.489
KOOS score, %		96.7±6.0	42.3±7.7	**0.000**
Speed, *m/s*	**SOS SS Ascending**	0.53±0.08	0.49±0.12	0.364
	SOS CS Ascending	0.59±0.02	0.57±0.04	0.107
	SBS Ascending	0.36±0.04	0.38±0.03	0.203
	SOS SS Descending	0.57±0.09	0.49±0.11	0.057
	SOS CS Descending	0.60±0.03	0.56±0.08	0.154
	SBS Descending	0.34±0.05	0.36±0.04	0.303

SOS SS and SOS CS correspond, respectively, to the Step-Over-Step at self-selected speed and at controlled speed and SBS to Step-By-Step.
Statistically significant differences ($p < 0.05$) between the two groups of subjects, evaluated by the independent *t*-test, are indicated in bold.

1.3.2 Data Collection Protocols

Motion Analysis

Protocol 1 used in Leuven

An active 3D motion analysis system (Krypton, Metris) recorded the 3D position of 27 light emitting diodes (LED) attached to the subjects according to an extended (5 technical clusters and 12 LED on 6 anatomical landmarks) Helen Hayes protocol (David *et al.*, 1991) (Figure 1.4 and 1.6) at a sampling frequency of 100 Hz. A force plate (Bertec Corporation, USA), embedded in the middle of the walkway, measured GRF and it was sampled at 1000 Hz. For step-up-and-over, the step was placed over the force plate. Five technical clusters of 3 markers each, were attached bilaterally to the lateral thighs and shanks, and posterior to the pelvis. The remaining 12 markers were fixed bilaterally on 6 anatomical landmarks: anterior superior iliac spine, lateral femoral epicondyle, lateral malleolus, calcaneus, fifth metatarsal head and midfoot.

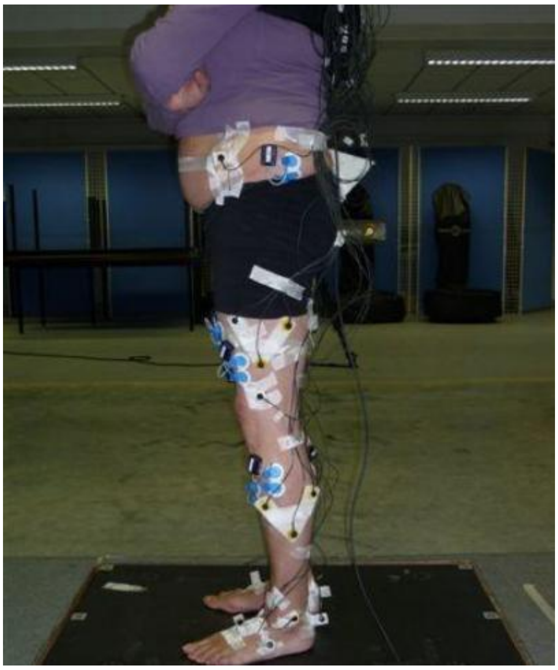

Figure 1.4 - LED markers and EMG sensors placement on a representative subject.

Gait analysis consisted of level barefoot walking along a 10 m walkway at self-selected speed. A total of 6 stance trials were averaged for each leg.

Step-up-and–over analysis consisted of stepping onto a 20-cm-high step with one leg (stepping leg), while stepping over with the other leg (trailing leg) making contact on the other side of the step. The subjects performed a total of 3 trials for each leg.

Sit-to-stand-to-sit analysis consisted of standing up from a chair and sit on the chair again completing a total of 6 trials per leg.

Dynamic motion analysis consisted of repetitive active flexion-extension of the unloaded tibia with the femur kept stationary. A total of 3 trials were averaged for each leg.

Protocol 2 used in Manchester

Motion analysis consisted of barefoot stair walking and was performed while ascending and descending a staircase consisting of seven steps at self-selected speed. A 10-camera 3D motion capture system (Vicon) synchronized with four force platforms (embedded in the middle four steps of the staircase) recorded the 3D position of 34 reflective markers (31 on the lower body and 3 tracking the trunk motion) according to an extended lower-body plug-in-gait marker set (Davis *et al.*, 1991) (with additional three-marker clusters, and markers on medial femur epicondyles and medial malleoli markers and trunk) (Figure 1.5 and 1.9), at 100 Hz and measured GRF and it was sampled at 1000 Hz (Kistler). GRF were filtered using a second order Butterworth low pass filter, with cut-off level at 30Hz, and marker trajectories using a smoothing spline with cut-off at 6Hz.

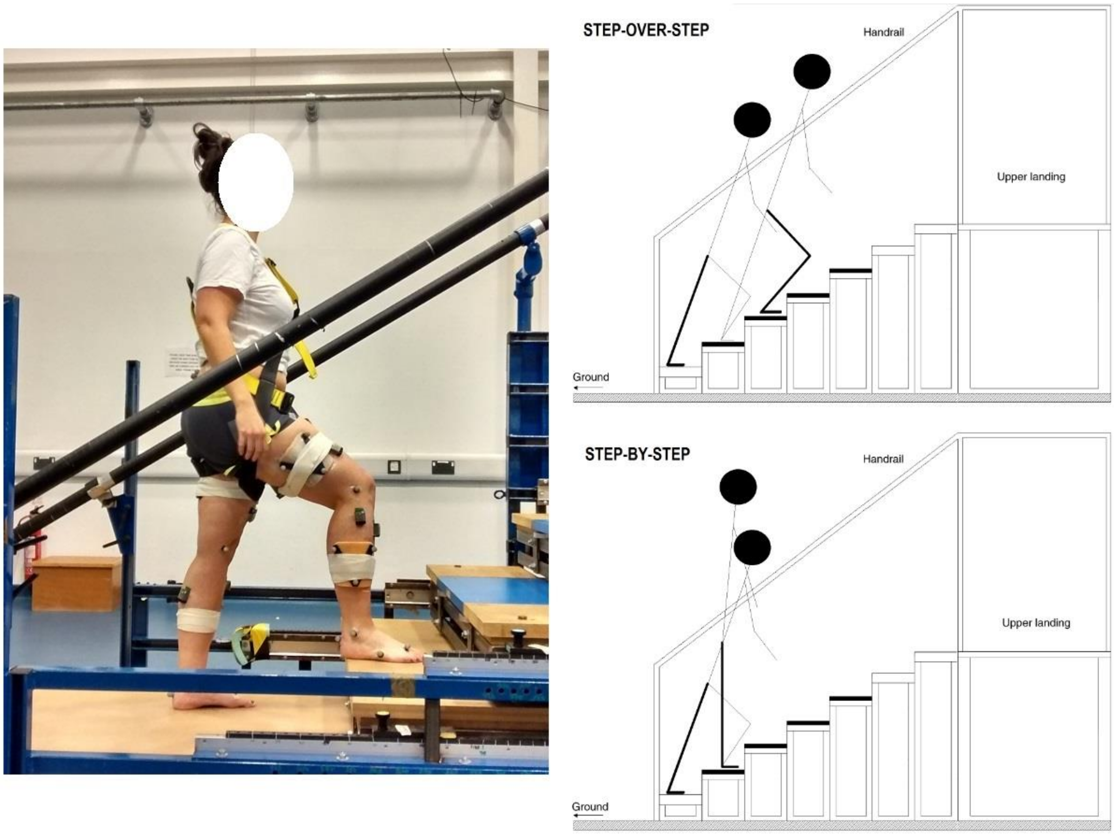

Figure 1.5 - Marker set on a representative subject while ascending the staircase (left) and a representative scheme of the step-over step (above right) and step-by-step (below right) tasks.

Patients were asked to ascend and descend a staircase of seven 17.2cm-height steps (Figure 1.5). Six trials per condition were collected for ascending and descending for three different conditions: step-over-step (SOS), i.e. alternating feet per step, while controlling their speed, via metronome with a cadence of 90 beats per minute, which has previously been shown to be close to the self-selected stair walking speed in healthy subjects (Spanjaard *et al*., 2007); and then two alternative strategies were tested: step-over-step (SOS) at their preferred (self-selected) speed; and step-by-step (SBS), i.e. both feet per step. The use of the handrail was not allowed. For safety reasons, patients wore a harness during the data collection.

Medical Imaging

Protocol 3 used in Leuven

The (most) affected side (clinical and structural) for OA subjects and a randomly chosen side for controls was selected for further analysis. MRI of the knee was performed in a 3.0-T scanner (Philips Achieva TX, Philips Medical Systems, Best, The Netherlands) using an eight-channel phased array knee coil in a non-weight-bearing supine position.

The imaging protocol consisted of sagittal and transversal proton density turbo spin echo (TSE) sequence images (36 slices, repetition time (TR)/echo time (TE)/slice thickness (ST)= 3,000ms/30 ms/2.5mm with 0.3-mm intersection gap), sagittal and coronal high resolution T2 TSE with fat saturation (26 slices, TR/TE/ST= 2,726ms/66ms/2.8mm), a sagittal three-dimensional (3D) gradient echo with different echo times (180 slices, TR/TE/ST= 26ms/9.2–15.3–21.4ms/0.5mm) and a sagittal 3D gradient echo with water-selective excitation (60 slices, TR/TE/ST= 20ms/5.2ms/1.5mm).

Protocol 4 used in Manchester

Scans were examined for any abnormalities indicating the presence of knee OA. For all participants, MRI of both knees were acquired in a 0.25-Tesla MRI scanner (G-scan, Esaote Biomedica, Genoa, Italy) in a non-weight-bearing supine position. A randomly chosen side for controls and the most painful knee for OA patients was also scanned in a weight-bearing prone position. The imaging protocol consisted of spin-echo TI half fourier (HF) sequence at the sagittal (15 slices, TR/TE/ST= 530ms/18ms/6mm) and frontal plane (76 slices, TR/TE/ST= 880ms/14ms/4mm).

1.3.3 Musculoskeletal Modeling

Workflow 1

The motion analysis was performed using the standard workflow in Opensim: the generic 3D musculoskeletal model of the lower body (Delp *et al.*, 1990) was extended to a 2 degrees of freedom knee joint, representing flexion/extension and adduction/abduction. Model pose estimation was computed by the *Inverse Kinematics*-based algorithm in which joint centers were calculated according to an extended (5 technical clusters and 12 LEDs on 6 anatomical landmarks) Helen Hayes protocol (Davis *et at.*, 1991). Basically, the static pose was computed by trying to match some combination of experimental marker positions and generalized coordinate values. Marker and coordinate weights were defined to determine how strongly the algorithm should try to match the experimental marker positions. Muscle actuators and wrapping objects were also scaled. And, different from *Direct Pose Estimation* method, IK-based algorithm allows the muscle-tendon length computation and a scale factor is computed to be used to scale the component’s length-dependent properties. In the generic OpenSim model, the flexion-extension knee axis is defined as the axis through the epicondyles (TEA). For **study I**, only this generic model was used. First, the model was scaled based on the marker positions and the subject's body mass (Figure 1.6). Thereafter, joint angles were calculated by inverse kinematics. Joint reaction forces and moments were obtained by inverse dynamics. As the human musculoskeletal joint is an indeterminate biomechanical system, where the number of unknown forces and moments generated by the muscles (and ligaments, if included in the model) as well as the joint reaction forces and moments exceed the equilibrium equations of the joint system, a unique solution for these unknows cannot be obtained. Therefore, optimization approaches can be used to predict the unknown individual muscle forces and joint reaction forces. An optimization routine is a powerful mathematical formulation for finding the “best available solution”, while maximizing or minimizing a certain function. A static optimization routine, was used to calculate muscle forces. Static optimization is an inverse dynamics-based routine uses the joint moments to calculate individual muscle forces that satisfy the moment equilibrium at each time frame by minimizing the sum of muscle activation squared. It minimizes the objective function:

$$J = \sum_{m=1}^{n} (a_m(t_i))^p$$

where *n* is the number of muscles in the model; a_m is the activation level of muscle *m* (limited between 0 and 1) at a discrete time instant (t_i); and, *p* is the power of the function. In order to improve the input kinematics on the muscle activations and forces, marker trajectories were filtered using a smoothing spline with cut-off at 6Hz. In order to reduce potential dynamic inconsistencies between the estimated model accelerations and the measured ground reaction forces, residual actuators were added to the origin of the pelvis segment, one actuator for each degree-of-freedom. These inconsistencies may result from marker measurement error, differences between the geometry of the model and the subject, and inertial parameters. Residual actuators were able to generate residual forces and moments up to 10N or Nm. Finally, KCF, resulting from the muscle forces and resultant forces were calculated during the stance phase. Specifically, joint forces and moments transferred between consecutive bodies as a result of all loads acting on the model are calculated. These forces and moments correspond to the internal loads carried by the joint structure.

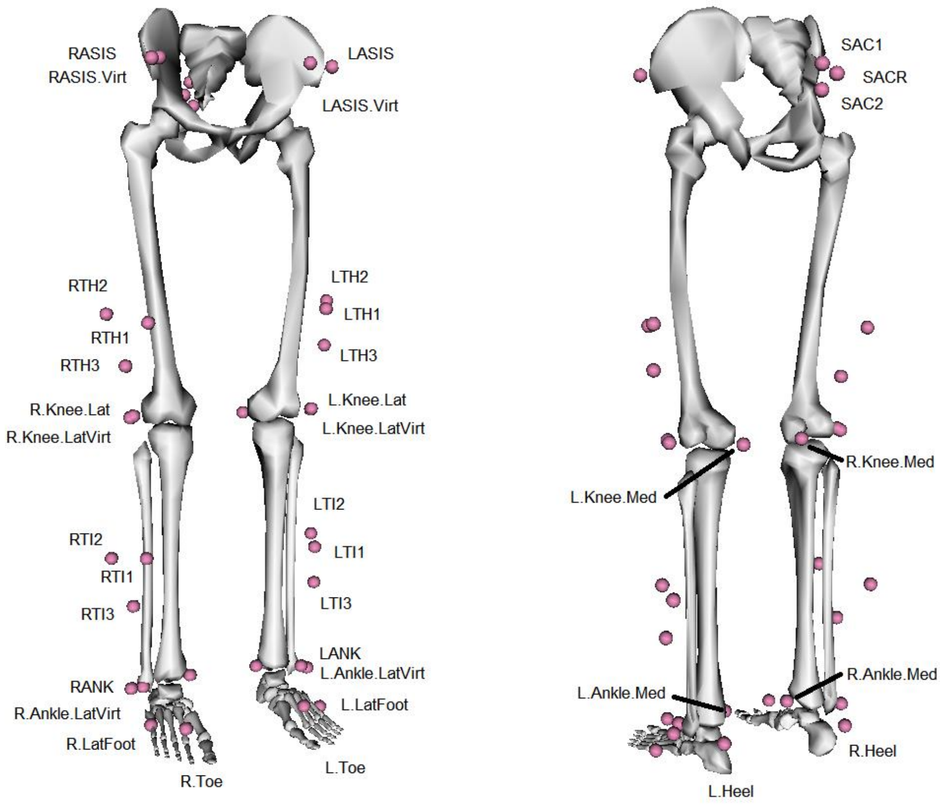

Figure 1.6 - Marker set used for Studies 1, 2 and 3. The markerset includes 31 markers attached to the lower body, consisting of a cluster of 3 markers on the sacrum (SACR, SAC1 and SAC2); anterior superior iliac spines (RASIS and LASIS); a cluster of 3 markers on the thigh (RTH1, RTH2 and RTH3, and LTH1, LTH2 and LTH3); knee (R.Knee.Med and R.Knee.Lat, and L.Knee.Med and L.Knee.Lat); a cluster of 3 markers on the tibia (RTI1, RTI2 and RTI3, and LTI1, LTI2 and LTI3); ankle (RANK and R.Ankle.Med, and LANK and L.Ankle.Med); heel (R.Heel and L.Heel); toe (R.Toe and L.Toe); and lateral foot (R.LatFoot and L.LatFoot).

For **study II**, three different models were used for each subject: one generic model with the TEA implemented; and two models with the FAR calculated by the SARA algorithm proposed by Ehrig *et al.* (2007) using a weight-bearing and non-weight-bearing motion as input conditions for the functional axis calculation. The stance phase of *step-up* motion was used as a weight-bearing motion and the swing phase of *step-up-and-over* motion was used as non-weight-bearing motion for calculating the two different FAR to generate the two models with FAR. The symmetrical axis of rotation approach (SARA) (Ehrig *et al.*, 2007) is a two-sided transformation technique, in which both segments (femur and tibia) are allowed to move. It calculates the orientation and the location defined by a fixed point on the axis expressed in the femur local coordinate system and the corresponding point expressed in the tibia local coordinate system by minimizing an objective function. This objective function defines the distance between these two points when they are expressed in the global coordinate system. Since the motion of the tibia relative to the femur is mainly aroung a single axis, this procedure results in a ser of point on a line. After its calculation, each FAR was implemented in the scaled model. The knee joint axis definition in the new OpenSim scaled models were, therefore, modified to reflect the calculated orientation and location of the FAR. In Figure 1.7 a representative generic model with TEA and a model with FAR at the knee joint are presented. Thereafter, joint angles were calculated by inverse kinematics and external moments were obtained by inverse dynamics.

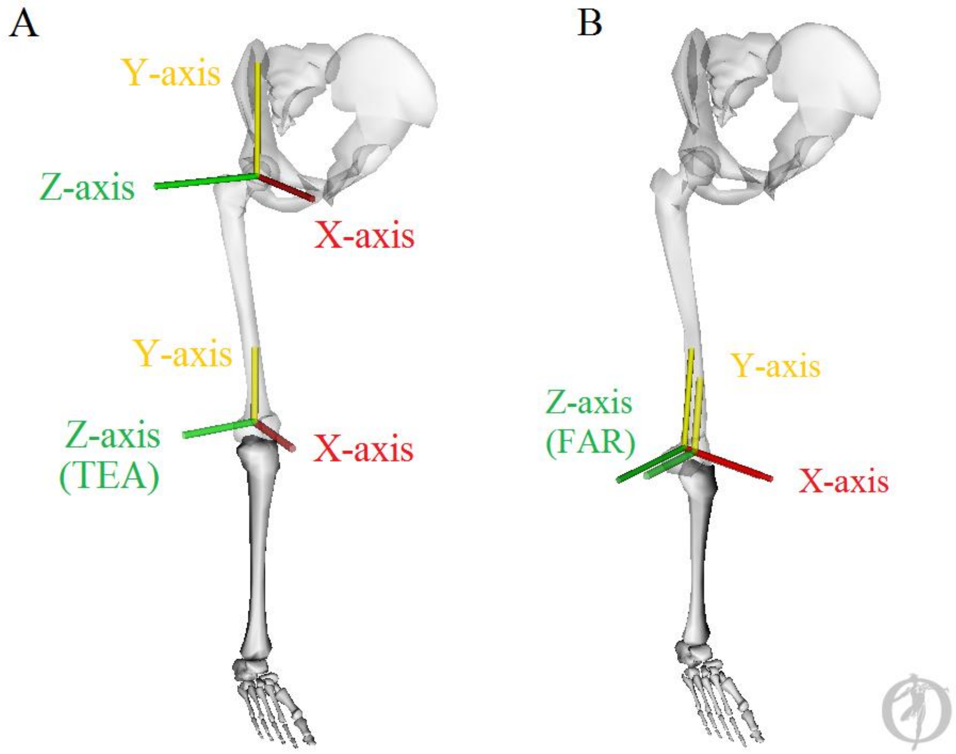

Figure 1.7 - OpenSim's musculoskeletal lower extremity generic model [23] including the knee joint reference frame relative to the femur and the tibia based on a transepicondylar axis (A) and a functional axis (B).

Workflow 2

A multi-body knee model (Figure 1.8) with 6 degrees of freedom (DoF) for the tibiofemoral and patellofemoral joints was used (Lenhart *et al.*, 2015). Fourteen ligaments were represented by bundles of nonlinear elastic springs. Cartilage surface contact pressures were computed using an elastic foundation formulation (Bei and Fregly, 2004; Lenhart *et al.*, 2015). The knee model was integrated into an existing lower extremity musculoskeletal model (Arnold *et al.*, 2010), which included 43 muscles acting about the hip, knee and ankle joints.

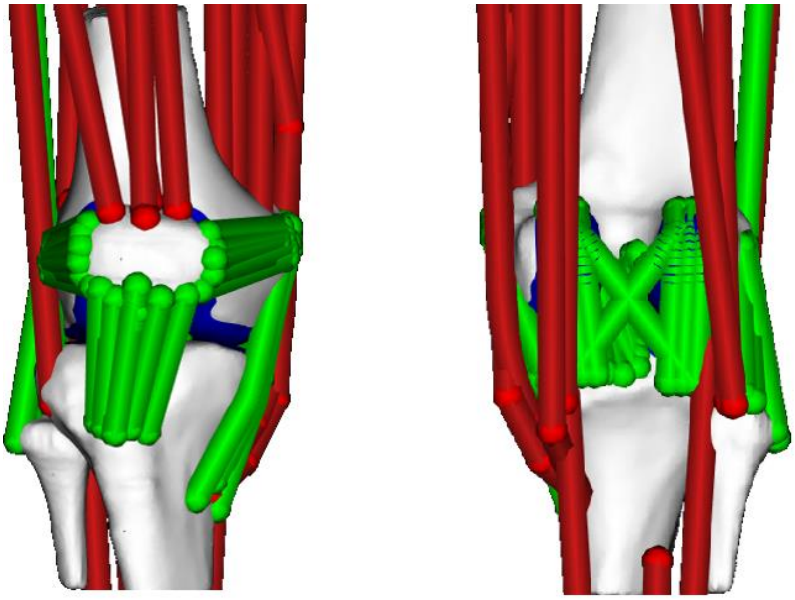

Figure 1.8 - Multibody 12 DoF knee model including ligaments and an elastic foundation contact model (Lenhart et al., 2015).

The lower extremity model was scaled to subject-specific segment lengths as determined in a static calibration trial. The joint angles were computed using an inverse kinematics algorithm. The concurrent optimization of muscle activations and kinematics (COMAK) algorithm (Lenhart *et al.*, 2015; Smith *et al.*, 2016), was used to compute the secondary tibiofemoral (angles in the frontal and transversal planes, and translations) and patellofemoral kinematics, muscle and ligament forces, and contact forces by minimizing the muscle volume weighted sum of squared muscle activations plus the net knee contact energy. The elastic foundation model

(Bei and Fregly, 2004) calculated the tibiofemoral contact pressures and the locations of the centre of pressures (CoP). Subsequently, an inverse dynamics algorithm computed the external joint moments in the three planes of motion.

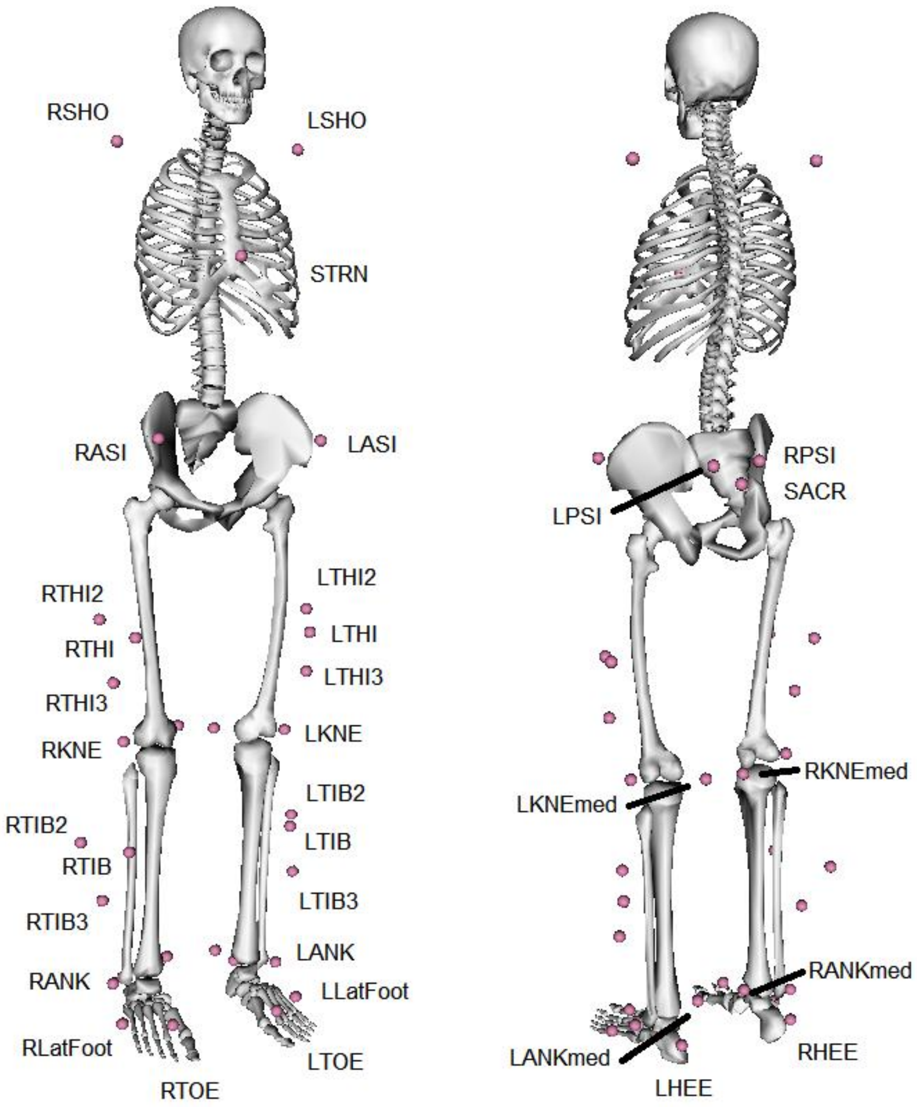

Figure 1. 9 - Marker set used for Study 4. The markerset includes 34 markers attached to the lower body, consisting of two markers on the acromion (RSHO and LSHO); one on the sternum (STRN); a one marker on the sacrum (SACR); posterior superior iliac spines (RPSI and LPSI); anterior superior iliac spines (RASI and LASI); a cluster of 3 markers on the thigh (RTHI, RTHI2 and RTHI3, and LTHI, LTHI2 and LTHI3); knee (RKNEmed and RKNE, and LKNEmed and LKNE); a cluster of 3 markers on the tibia (RTIB, RTIB2 and RTIB3 for the right, and LTIB, LTIB2 and LTIB3 for the left); ankle (RANK and

RANKmed, and LANK and LANKmed); heel (RHEE and LHEE); toe (RTOE and LTOE); and lateral foot (RLatFoot and LLatFoot).

1.3.4 Data analysis

The respective parameters calculated for each study are presented in Table 1.6.

Table 1. 6 – Overview of the different workflow steps used for each study.

	IK (Joint angles)	ID (Knee external moments)	Optimization (Muscle Forces)		ID after COMAK	KCF	CP	CoP
			SO	COMAK				
Study I	X	X	X			X		
Study II	X	X						
Study III	X			X	X	X	X	X
Study IV	X			X	X	X	X	X

IK corresponds to inverse kinematics; ID to inverse dynamics; SO to static optimization; COMAK to concurrent optimization of muscle activations and kinematics; KCF to knee contact forces; CP to contact pressures; and CoP to centre of pressure on the tibia.

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Chapter 2

Knee contact forces are not altered in early knee osteoarthritis compared with healthy controls

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2.1 Introduction

Osteoarthritis (OA) is a chronic degenerative and multifactorial (Andriacchi *et al.*, 2004; Lories and Luyten, 2011) joint disease that most frequently affects the knee (Buckwalter and Martin, 2006). Patients complain about pain, reduced range of joint movement, muscle weakness, stiffness and instability, which limits physical activities in daily living (Bhatia *et al.,* 2013), results in loss of their independence, reduced quality of life and high health-related costs (Fitzgerald *et al.,* 2004).

The cause of OA remains unclear. It is known that biochemical and mechanical factors may contribute to its initiation (Brandt *et al*., 2003; Goldring and Goldring, 2007; Liikavaino, 2010; Radin and Rose, 1986). Indeed, subchondral bone remodeling (Burr, 2004) following mechanical overloading will increase the reactive stresses underneath the cartilage, therefore decreasing the shock absorbing efficiency of cartilage (Runhaar *et al*., 2011) and causing local cartilage lesions (Henriksen, 2007). In agreement with this statement, aberrant knee joint loading has been identified as a factor affecting the progression of knee OA (Nuki and Salter, 2007; Sharma, 2001; Brouwer *et al*., 2007) in more advanced stages of OA (Foroughi *et al.,* 2009): increased medial compartment loading has been associated with more pronounced clinical symptoms and OA severity as assessed by radiography (Baliunas *et al*., 2002; Baert *et al*., 2013). Most studies (Lewek *et al.,* 2004; Andriacchi, 1994; Fregly *et al*., 2007; Mundermann *et al*., 2008; Hurwitz *et al*., 2000; Guo *et al*., 2007; Miyazaki *et al*., 2002; Baliunas *et al*., 2002) used the knee adduction moment (KAM), i.e. the external knee joint moment in the frontal plane was used as an indirect measure of medial compartment loading during functional activities. Alternatively, musculoskeletal modeling in combination with dynamic motions has been used to calculate knee contact forces (KCFs). Using this approach, Kumar *et al.* (2013) found medial KCF were increased in established OA subjects (K&L ≥ 2) with radiographic signs of joint structural changes. Interestingly, medial compartment loading of the knee was found to be related to a combination of both KAM and knee flexion moment (KFM), therefore questioning the role of KAM as sole indicator of medial compartment knee loading.

More recently, clinical interest is towards identifying OA patients in more early stages of the disease process. Early detection of OA may enable more effective interventions before major structural damage has occurred (Guermazi *et al*., 2012). The lack of effectiveness in delaying the progression of OA (McAllindon *et al*., 2014) may be mainly caused by a late intervention, when structural deterioration is already advanced (Felson and Hodgson, 2014). Luyten *et al.* (2012) have proposed a classification criteria for identifying early knee OA patients, which combines knee pain and Kellgren and Lawrence (K&L) radiographic classification (0 or 1) (Kellgren and Lawrence, 1957) with structural changes detected on Magnetic Resonance Imaging (MRI) or cartilage lesions by arthroscopy.

The role of mechanical loading in these patients where only early signs of joint degeneration are present, is less well explored in literature. Three recent articles have shown that there is no evidence of increased KAM in early stages of knee OA compared to healthy controls (Foroughi *et al.,* 2009; Baert *et al*., 2013; Duffell *et al*., 2014). However, since KAM does not account fully for the internal knee joint loading (Kumar *et al*., 2013; Meyer *et al*., 2013), these studies potentially fail to describe the more subtle changes in loading characteristics in the early OA patients where structural degeneration is less pronounced.

The current study is therefore the first study to evaluate whether knee loading as assessed by KCF, is different in subjects with early medial knee OA compared to healthy subjects and subjects with established medial knee OA. It is hypothesized that in the presence of early signs of structural degeneration as present in early OA subjects, knee loading is increased compared to healthy subjects but to a lesser extent than in established OA subjects. If so, this would confirm that biomechanical overloading is a contributing factor to the progression of OA from the very early onset of the disease. Furthermore, if subjects with early OA present increased knee loading will confirm KCF to be a more sensitive biomarker than KAM in detecting alterations in knee loading in early stages of OA, allowing evaluation of treatment effect even in early stages of the disease process and allowing for earlier interventions.

Furthermore, this study evaluates the contribution of altered frontal and sagittal plane moments to the observed changes in knee loading for subjects in different stages of the disease process. It is hypothesized that in early OA patients, presenting limited structural degeneration, frontal plane moments will contribute less to the observed changes in knee loading compared to the established OA group. If so, alterations in mechanical knee loading, associated with different levels of joint degeneration, relate to alterations in multidimensional joint loading, with KAM being a more important contributor compared to KFM in patients with established knee OA will be confirmed.

2.2 Methods

Participants

Fifty-nine participants (all women, mean age of 65±7.3 years) were recruited for this study and were separated into three groups based on a previously published classification (Luyten *et al*., 2012): control subjects (*n*=20), early medial knee OA (*n*=16), and established medial knee OA (*n*=23) patients. Subject characteristics are listed in Table 1. All procedures were approved by the local ethical committee of Biomedical Science, KU Leuven, Belgium. Written informed consent was obtained from each subject.

Early medial knee OA was diagnosed based on novel classification criteria of Luyten et al. (2012), including fulfillment of three criteria, namely knee pain, a K&L (Kellgren and Lawrence, 1957) grade 0, 1 or 2^{-} (osteophytes only) and structural changes observed on MRI.

Established medial knee OA was diagnosed based on slightly adapted American College of Rheumatology classification criteria (Altman *et al*., 1986), including knee pain, stiffness less than 30 min and crepitus, together with structural changes defined as presence of minimum grade 2^{+} (osteophytes and joint space narrowing) on K&L scale for at least the medial compartment on radiography.

A control group was also analyzed, which included asymptomatic healthy subjects with no history of knee OA or other pathology involving any lower extremity joints, and with a radiological score of 0 or 1 according to K&L score.

Participants were excluded if they had a prior significant trauma or surgery in lower limbs and/or low back, if they suffered from a neurological disease affecting coordination and/or balance during gait and/or a musculoskeletal disorders other than knee OA in one of the limbs during the last six months prior to testing.

For symptomatic patients with unilateral knee OA (*n*=9), only data of the affected knee were analyzed. For those with bilateral knee OA and with large asymmetry in severity (*n*=7), the most affected side was selected for further analysis. For all other subjects (*n*=23), both legs were analyzed.

Gait analysis

An active 3D motion analysis system (Krypton, Metris) recorded the 3D position of 27 LEDs attached to the subjects according to an extended (5 technical clusters and 12 LEDs on 6 anatomical landmarks) Helen Hayes protocol (David *et al.*, 1991) at a sampling frequency of 100 Hz (Figure 2.1).

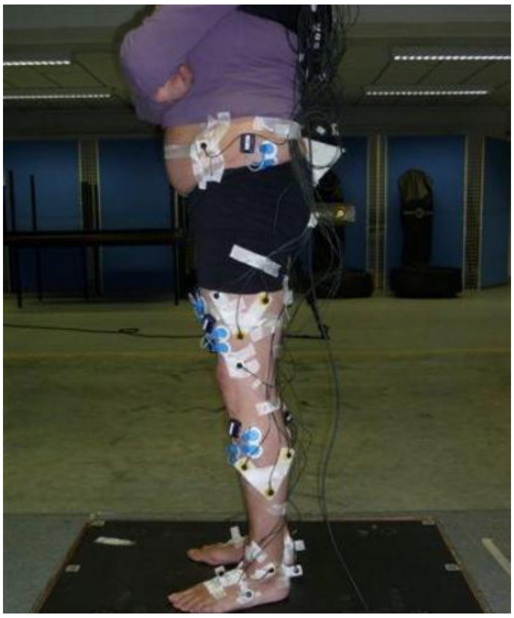

Figure 2.1 - LED and EMG sensors placement on a representative subject.

Gait analysis consisted of level walking along a 10 m walkway at self-selected speed. A total of 12 stance trials were averaged for controls and also for patients with bilateral OA with similar severity classification for both legs and 6 for the patients who had a less/no affected leg. Barefoot walking was chosen in order to optimize standardization since variation in footwear would influence lower limb loads (Shakoor and Block, 2006).

Marker data were labeled and smoothed using a spline routine (Woltring, 1986) in Matlab (Mathworks, inc.). The remainder of the analysis was performed using the standard workflow in Opensim (Delp *et al*., 2007): the 3D musculoskeletal model of the lower body (Delp *et al*., 1990) was extended with a 2 degrees of freedom knee joint: flexion/extension and adduction/abduction. First, the model was scaled based on the marker positions and the subject's body mass. Thereafter, joint angles were calculated by inverse kinematics. Joint reaction forces and moments were obtained by inverse dynamics. Knee joint moments were normalized to body weight and height (%BWHt, $N/kg.ms^{-2}$). A static optimization routine (Anderson and Pandy, 2001) that minimizes the sum of muscle activation squared was used to calculate individual muscle forces. Finally, KCF, resulting from the muscle forces and resultant forces were calculated during stance phase. KCF are expressed relative to the tibia reference frame with the origin in the knee joint center and normalized to body weight (BW, $N/kg.s^{-2}$). All data were time normalized to stance phase, from initial contact (heel strike) to toe-off.

Data analysis

Maximal total KCF, KAM and KFM during the first and second half of the stance phase and minimum values of the same parameters during the single support (SS) phase were determined.

Given the decreased walking speed (Kaufman *et al*., 2001) and concomitant prolonged stance phase (Al Zahrani and Bakheit, 2002; Gok *et al*., 2002) present in patients with OA, the KAM and KFM angular impulse and KCF impulse were also analyzed. These correspond to the time integral of the moments and the total KCF and account for changes in both load magnitude and duration.

Statistical analysis

One-way analysis of variance (ANOVA) with Gabriel post hoc test (SPSS Inc., v17.0) evaluated whether differences in peak KCFs, KAMs and KFMs as well as their impulses were significantly different ($p \leq 0.05$).

To investigate the contribution of KAM and KFM to the KCF, values of KAM and KFM at the three time instants of peaks and SS were correlated to KCF. First, coefficient of determination (R^2) between KAM and KCF, and between KFM and KCF was calculated in order to assess how much variance in KCF was explained by KAM and KFM, respectively. Multiple regression was then calculated to assess how much variation in KCF was explained by the combination of KAM and KFM. A linear relationship was assumed between KAM and KCF, KFM and KCF, and, finally, between KAM together with KFM and KCF. Multicollinearity between KAM and KFM was verified for peaks and SS by the variance inflation factor (VIF) and tolerance (T) values (Fiedl, 2009; Bowerman and O'Connell, 1990) and was found to be negligible (Table 2.1).

Table 2. 1 - Results for assessing the assumption of no multicollinearity between KAM and KFM as predictors of peak KCFs and minimum KCF during single support phase (Tolerance and VIF).

		Control	Early OA	Established OA	All Subjects
P1	**Tolerance**	0.987	0.812	0.939	0.958
	VIF	1.013	1.232	1.065	1.043
P2	**Tolerance**	0.893	0.841	0.826	0.872
	VIF	1.120	1.189	1.210	1.147
SS	**Tolerance**	0.892	0.701	0.939	0.940
	VIF	1.121	1.428	1.065	1.064

P1 and P2 correspond, respectively, to first and second peak. SS corresponds to the minimum value during the single support phase.

2.3 Results

Subject characteristics

Age, body mass, gait speed, stance duration and timing of the peak KCF did not differ significantly between the three groups (Table 2.2). Single support phase was significantly shorter in patients with established OA compared to control subjects (p = 0.040). Significantly higher varus alignment was observed in patients with established OA compared to the control group (p = 0.022).

Table 2. 2 - Characteristics of the groups: control (C0), early OA (EA) and established OA (ES).

	Control (*n* = 20)	**Early OA (*n* = 16)**	**Established OA (*n* = 23)**	***p***	***p* (CO-EA)**	***p* (CO-ES)**	***p* (EA-ES)**
Age, *years*	64.6±8.7	64.9±6.0	65.6±7.2	0.910	0.999	0.965	0.989
Body mass, *kg*	65.0±8.0	70.5±14.0	73.2±12.8	0.079	0.417	0.076	0.860
Gait speed, *m/s*	1.23±0.20	1.29±0.19	1.21±0.14	0.338	0.659	0.963	0.373
Stance Duration, *s*	0.63±0.07	0.63±0.06	0.64±0.06	0.096	0.871	0.366	0.105
Timing of the peak KCFs, *% Stance*	29.1±2.0	28.4±2.1	29.3±2.2	0.400	0.716	0.971	0.448
	82.9±2.6	83.0±4. 9	80.2±5.7	0.095	1.000	0.174	0.189
Single Support Duration, *% Stance*	61.7±3.9	61.2±2.8	60.1±4.2	0.041*	0.832	**0.040***	0.287
Knee Alignment, ^{o}	-.03±2.15	0.37±3.31	2.77±4.30	0.020*	0.965	**0.022***	0.067
No. of legs	36	30	32		-	-	-
KL grade (no. of legs)	0(24) 1(12)	0(8) 1&1^+ (22)	2^+(22) 3&3^+ (5) 4(4)		-	-	-

Values are the mean ± Standard Deviation (SD). ANOVA with Gabriel *post hoc* test.
Significant difference p < 0.05 are indicated with *.
Positive values indicate varus alignment and negative values indicate valgus alignment.

Knee joint loading

First peak KAM was significantly different between groups (p = 0.038). However, although higher KAM was observed in established OA patients (Figure 2.2), no significant differences were found when pairwise comparisons were done. Peak KFMs were not significantly different between any of the three groups. In contrast, significant lower KFM (p = 0.013) was found during SS in early OA when compared to established OA.

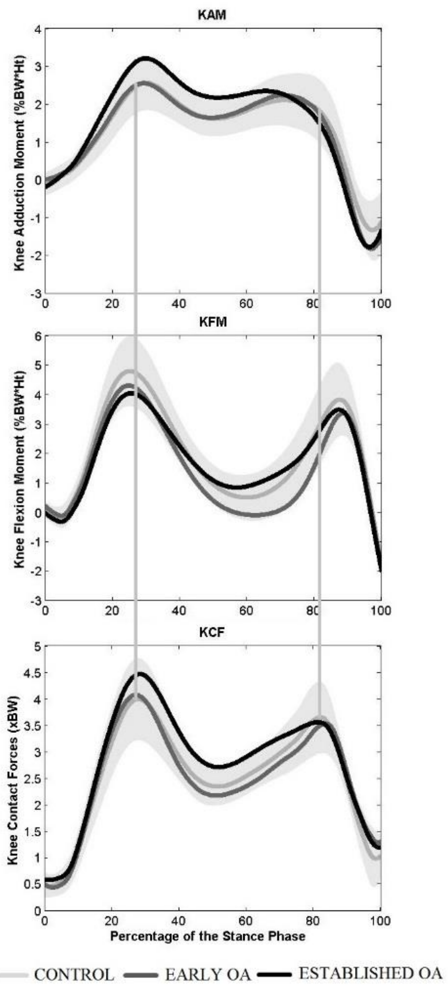

Figure 2. 2 - Average KAM, KFM and KCF during stance phase in the 3 groups with vertical lines indicating the time instants of peak KCFs in the control group.

KCF is highest during the first peak, in all patient groups, particularly in patients with established OA. However, no statistically significant differences were found between the groups in terms of first and second peak KCFs (Table 2.3). During midstance (SS), the early OA group showed significantly lower KCF compared to established OA (p = 0.022).

KAM and KFM angular impulses did not significantly differ between groups (Table 2.4). However, KCF impulses were significantly increased in established OA subjects when compared to control group (p=0.033) and early OA (p=0.018).

Table 2. 3 - Peak and SS values of the KCF, KAM and KFM during the stance phase of the gait cycle for control (CO), early OA (EA) and established OA (ES) groups.

		Control	Early OA	Established OA	*p*	*p* (CO vs EA)	*p* (CO vs ES)	*p* (EA vs ES)
P1	**KAM**	2.59±0.69	2.59±0.90	3.22±1.06	**0.038***	1.000	0.074	0.099
	KFM	4.83±1.18	4.38±1.61	4.12±2.03	0.380	0.807	0.420	0.948
	KCF	4.03±0.77	4.12±0.96	4.49±1.04	0.243	0.989	0.302	0.532
P2	**KAM**	2.21±0.71	2.40±0.66	2.40±0.87	0.666	0.838	0.803	1.000
	KFM	3.90±1.27	3.41±1.09	3.58±1.08	0.429	0.500	0.747	0.954
	KCF	3.71±0.67	3.64±0.59	3.72±0.62	0.933	0.984	1.000	0.980
SS	**KAM**	1.54±0.47	1.55±0.62	1.91±0.91	0.175	1.000	0.294	0.400
	KFM	0.42±0.75	-.25±0.87	0.73±1.26	**0.016***	0.158	0.970	**0.013***
	KCF	2.29±0.35	2.13±0.55	2.65±0.73	**0.019***	0.788	0.131	**0.022***

* Statistically significant ($p < 0.05$), *post-hoc* Gabriel calculated by ANOVA. KAM and KFM expressed as mean ± SD (%BW*Ht), and KCF as (mean ± SD (BW)), where SD is standard deviation. P1 and P2 correspond, respectively, to first and second peak and SS to the minimum value during the single support phase.

Table 2. 4 - Total KCF impulses (KCFi), and KAM and KFM angular impulses (KAMi and KFMi, respectively) in control (CO), early OA (EA) and established OA (ES) during the whole stance phase of the gait cycle. Significances are also reported.

	Control	Early OA	Established OA	*p*	*p* (CO *vs* EA)	*p* (CO *vs* ES)	*p* (EA *vs* ES)
KCFi	1.64±0.14	1.61±0.23	1.84±0.32	**0.008***	0.976	**0.033***	**0.018***
KAMi	0.86±0.26	0.83±0.36	1.00±0.46	0.327	0.996	0.541	0.452
KFMi	1.26±0.36	0.92±0.48	1.16±0.66	0.166	0.177	0.912	0.419

* Statistically significant ($p < 0.05$), *post-hoc* Gabriel. KCF impulses are expressed as mean ± SD (BW*s), KAM and KFM angular impulses as mean ± SD (%BW*Ht*s), where SD is standard deviation.

Coefficient of determination between external knee moments and internal KCF

During first peak and SS, KAM correlates significantly to KCF ($p < 0.01$) in both patient groups, with the highest contribution in the established OA subjects (up to 74%, Table 2.5). Although lower contributions were found for KFM compared to KAM, the contributions of KFM were higher in the OA groups compared to controls with the highest contribution in early OA subjects (up to 62%). The combination of KAM and KFM better predicted KCF, increasing the prediction up to 91% and 95% in the patient groups.

Table 2. 5 - Coefficients of determination (R^2 values (%)) for KCF fitted as a function of corresponding KAM or KFM and coefficients of determination (R_m^2 values (%)) for KCF fitted as a function of corresponding KAM+KFM for the first and second peak, and the minimum peak (during single support phase) in KCF.

		Control		**Early OA**		**Established OA**	
		KAM	**KFM**	**KAM**	**KFM**	**KAM**	**KFM**
P1	R^2	65.1**	20.6*	68.6**	62.1**	73.7**	38.2**
	R_m^2	85.7**		91.2**		91.2**	
P2	R^2	18.9	25.5*	0.0	54.5**	5.0	6.8
	R_m^2	66.0**		65.4**		20.2	
SS	R^2	42.0**	4.7	89.6**	46.7**	86.2**	26.3*
	R_m^2	62.7**		93.5*		94.8**	

* Statistically significant ($p < 0.05$) and ** ($p < 0.01$) contribution that causes R^2 to change by the inclusion of one predictor (KAM or KFM for simple correlation) or by the inclusion of new predictors (KFM for the multiple regression). R_m^2 is the coefficient of determination of the multiple regression. P1 and P2 correspond, respectively, to first and second peak, and SS to the minimum value during the single support phase.

At the time instant of the second peak KCF, KAM did not predict KCF in both patient groups. KFM contributed only significantly ($p < 0.01$) to KCF in the early OA group (variance predicted 55%). In early OA, the variance of the KCF accounted for when combining KFM and KAM was similar to that in control subjects. In contrast, in patients with established OA, the variance in KCF explained when combining KAM and KFM remained very low (20%).

2.4 Discussion

This study investigated mechanical knee loading in terms of external moments (KFM and KAM) as well as KCF during gait in subjects with early knee OA compared to controls and established knee OA using musculoskeletal modeling and simulations of motion. We aimed to investigate the presence of altered knee joint loading in early knee OA where structural degeneration is limited compared to established OA as well as the extent to which alterations in the frontal and sagittal plane moments contribute to the observed changes in knee loading.

Mechanical loading was not significantly higher in early OA subjects compared to controls, not when considering the external moments (KAM or KFM), nor knee contact forces. This finding falsifies the first hypothesis. From this we conclude that no signs of increased knee loading are present in subjects that only present early signs of structural joint degeneration. These findings are in line with Baert *et al.* (2013) and Duffell *et al.* (2014), who found no differences in KAM between early OA and healthy subjects. Therefore, the potential use of knee contact forces during walking to detect treatment effect on early OA was not confirmed. However, it is important to recognize that only walking has been evaluated in this study and that this may not be representative for an overall functional status of the subjects. Indeed, Hensor *et al.* (2015) reported knee pain first during weight-bearing activities involving deep knee bending, such as climbing or descending stairs, since they are more challenging. Future research should therefore focus on studying knee loading during these more demanding tasks as they may be more sensitive in detecting early changes in knee loading in OA subjects.

Mechanical loading was higher in established OA compared to early OA subjects. Indications for higher knee loading were statistically confirmed for increased knee contact force impulses. These were significantly higher in the established compared to the early OA subjects, representative for the cumulative effect of increased loading magnitude and prolonged stance duration in the established OA group. It is important to note that in the current groups, increased loading was not statistically confirmed when only considering the peak knee contact forces or the peak external joint moments. The tendency of increased KAM and KCF is in line with the results of Baert *et al.* (2013), Kumar *et al.* (2013) and Richards *et al.* (2010). However, loading during single stance was significantly increased in established OA as reflected in the higher KCF and KFM during single stance. These findings are in line with the reported changes in KFM during single stance reported in the study of Baert *et al.* (2013). These findings partially confirm the first hypothesis and further support the presence of increased loading in later stages of OA where more structural joint degeneration is present.

KCF relates to the multidimensional contribution of the external moments of the knee joint. A good prediction of the variance in KCF during the first peak, where the knee contact force magnitude is maximal, is found for all groups when considering KAM and KFM. Although during initial double support, knee loading is predicted well by KAM irrespective the presence of OA, multiple regression results show that a combination of KAM and KFM leads to a better prediction of KCF than KAM or KFM alone, which is in agreement with previous studies (Kumar *et al*., 2013; Walter *et al*., 2010). Therefore, in agreement with our second hypothesis, we can conclude that both frontal and sagittal plane moments need to be considered to estimate KCF.

However, in established OA patients, the variance accounted for when combining KAM and KFM is low (20%) during second part of the stance phase. This highlights the important role of muscle action controlling flexion-extension and adduction-abduction moments in joint loading during late stance.

With increased structural joint degeneration, peak mechanical knee loading is differently influenced by the frontal and sagittal knee moments. When initial structural degeneration is present, KFM contributes more to the KCF. When structural degeneration increases, the contribution of KAM increases.

Except for the second half of stance, where KAM could not predict the peak KCF.

Limitations of this study

These results have to be interpreted in view of certain methodological limitations. Ligaments were not included, assuming that external moments are generated entirely by the muscle-tendon structures. For that reason, the KCF is calculated without differentiating between medial and lateral compartment. In the current approach, the same control strategy (minimal effort) for controls and OA patients was assumed. In future research, passive and ligamentous structures will be incorporated in EMG-constrained muscle force computation.

2.5 Conclusions

Based on the followed modeling approach, excessive mechanical loading is not present during gait in early stages of OA but only in established OA compared to controls. This suggests excessive loading is not a contributor to early progression of OA, but may only result after later structural degeneration. Furthermore, KFM was essential to estimate KCF during the second peak in early OA. Therefore, KAM combined with KFM (rather than KAM on its own) is necessary to better estimate KCF and therefore might be used as feedback signal during gait retraining sessions aimed at assessing knee loading in patients with knee osteoarthritis. However, caution is required when assessing changes in KCF from changes only at the level of external moments in established OA patients, especially during the second half of the stance.

Author contributions

All authors take responsibility for the integrity of the work as a whole, including data and accuracy of the analysis. Conception: S. Meireles, F. De Groote, ND. Reeves, I. Jonkers. Design: S. Verschueren. All the authors contributed to the analysis and interpretation of the data, drafting of the article and final approval of the article.

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Competing interests

All authors declare no conflict of interest.

2.6 References

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Chapter 3

Differences in knee adduction moment between healthy subjects and patients with osteoarthritis depend on the knee axis definition

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3.1 Introduction

Gait analysis has been widely used to assess changes in the kinematics and kinetics of weight-bearing joints in degenerative disorders such as osteoarthritis (OA). In patients with knee OA, changes in joint loading during gait have been evaluated indirectly using the knee adduction moment (KAM), whereby increased KAMs have been related to OA progression (Andriacchi, 1994; Fregly *et al*., 2007; Mundermann *et al*., 2008; Hurwitz *et al*., 2000; Guo *et al*., 2007; Miyazaki *et al*., 2002; Baliunas *et al*., 2002; Lewek *et al*., 2004). Many studies (Newell *et al*., 2008; Ogaya *et al.,* 2014; Levinger *et al,* 2013; Thorp *et al.*, 2006; Thorp *et al*., 2007; Astephen *et al*., 2008; Landry *et al*., 2007) on knee loading in OA used the transepicondylar axis (TEA), i.e. the axis defined between markers placed on the medial and lateral epicondyle prominences, to describe the joint axis of rotation (AoR). However, this method relies on manual palpation of external anatomical landmarks, which, when placed incorrectly, can easily lead to errors in calculating the frontal plane angles in the presence of knee flexion, the so-called "cross-talk" phenomenon (Robinson and Vanrenterghem, 2012). Therefore, this may introduce uncertainty and different results in the KAM.

The functional axis of rotation (FAR) is less commonly used when studying knee joint loading in patients with OA. The FAR is a motion-based AoR, whose orientation and location represent the averaged orientation and location of the instantaneous ARs during knee motion (Schwartz *et al.,* 2007). FAR reduces the cross-talk effect on the knee kinematics in healthy and arthritic subjects (Van Campen *et al.,* 2011). Although knee kinetics computed using FAR and TEA have been compared during gait and side-cutting (Baudet *et al*., 2014) in healthy subjects, the difference between both is still unknown in subjects with knee OA. Furthermore, it is unclear whether FAR should be calculated based on weight-bearing or non-weight-bearing motion. This is highly relevant as passive laxity (Lewek *et al*., 2004) and lack of dynamic knee stability (Lewek *et al*., 2004; Fitzgerald et al., 2004) are present in patients with knee OA and this might have an important effect on the calculated AoR and consequently the calculated KAM.

In our previous work (Meireles *et al.,* 2016), knee loading was assessed in terms of KAM and knee contact force (KCF) by using an OpenSim modeling workflow in patients with early and established medial knee OA. Significant differences in the magnitude of the first peak KAM were found between the three groups. The current study was a secondary analysis of the aforementioned study (Meireles *et al.,* 2016). The purpose was threefold: firstly, to investigate the effect of using an anatomical versus a functional AoR on KAM in healthy subjects and patients with knee OA; secondly, to report the effect of using weight-bearing or non-weight-bearing motion to calculate the FAR on KAM; and finally, to assess whether the use of these different axes has an impact on the differences in KAM between healthy subjects and patients with knee OA. We hypothesize that (1) using TEA versus FAR will influence the differences in KAM between groups; (2) due to the presence of structural changes and unstable knee joints in patients with established OA, the KAMs calculated using FAR during weight-bearing motion are significantly different from those calculated using FAR during non-weight-bearing motion.

3.2 Methods

Participants

Patient selection and classification were described in Meireles *et al.* (2016). Briefly, fifty-nine female participants were divided into three groups (65±8.7, 65±6.0 and 66±7.2 years-old, respectively): (1) asymptomatic healthy subjects (*n*=20); (2) patients with early medial knee OA (*n*=16, presenting knee pain and structural changes only observed on MRI (Meireles *et al.,* 2016); and, (3) patients with established medial knee OA (*n*=23, presenting structural changes (Kellgren–Lawrence ≥2^+)). No significant differences in body mass index (BMI) were found between groups (25.0±3.0, 26.5±4.4 and 28.1±4.5, respectively, control, early OA and established OA).

Data collection

Data collection was described in Meireles *et al.* (2016). Body motion was measured using 27 active markers attached to the subjects according to an extended Helen Hayes protocol (David *et al*., 1991) recorded at 100 Hz. Five technical clusters of 3 markers each, were attached bilaterally to the lateral thighs and shanks, and posterior to the pelvis. The remaining 12 markers were fixed bilaterally on 6 anatomical landmarks: anterior superior iliac spine, lateral femoral epicondyle, lateral malleolus, calcaneus, fifth metatarsal head and midfoot. GRFs were collected at 1000 Hz using a force plate embedded in the ground (Bertec Corporation, USA).

Musculoskeletal Model

A generic musculoskeletal lower extremity model (OpenSim 3.0) was used in this study (Delp *et al.,* 1990). The model consists of eleven rigid-body segments, each defined by a local reference frame: a pelvis, left and right thigh, shank, talus, calcaneus and toes. Joints define the relative motion of two reference frames (Figure 3.1), one attached to the parent segment and one attached to the child segment that do not necessarily coincide with the segment local reference frames. In the generic model, the pelvis is modeled as a free joint with 6 degrees of freedom (DoF), the hip as a ball-in-socket joint with 3 DoF, the knee as a sliding hinge joint with 1 DoF and the ankle as a hinge joint with 1 DoF.

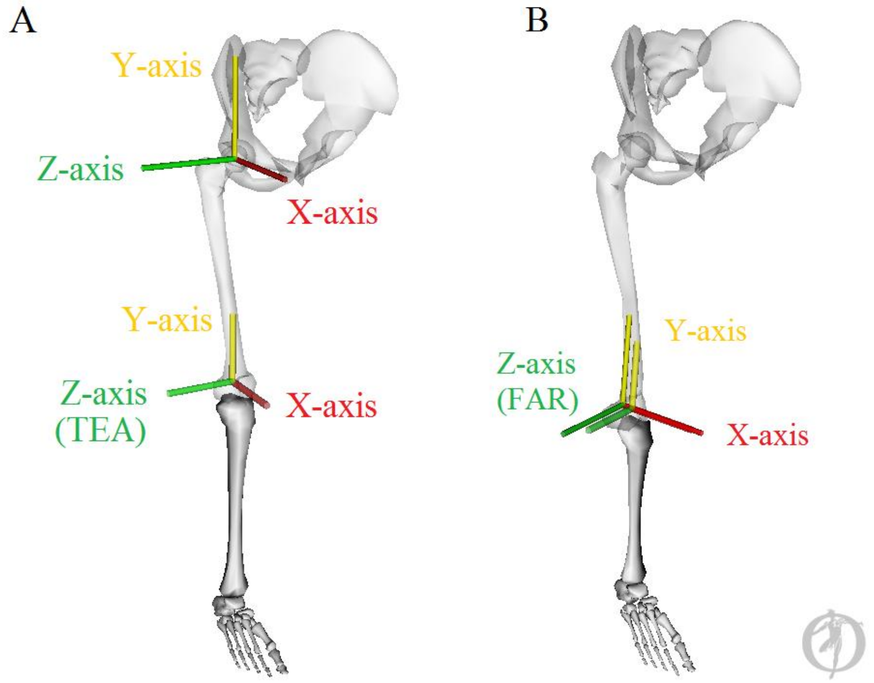

Figure 3. 1 - OpenSim's musculoskeletal lower extremity generic model [23] including the knee joint reference frame relative to the femur and the tibia based on a transepicondylar axis (A) and a functional axis (B).

The origin of the femoral reference frame (f_{RF}) is located at the hip joint centre (HJC, i.e. the centre of the femoral head). The axes of the f_{RF} are defined as follows: the Y-axis is oriented along the line passing through the midpoint of the epicondylar markers and the HJC, pointing superiorly; the Z-axis lies in the plane defined by the HJC and the epicondylar markers, and is perpendicular to the Y-axis, pointing to the right (laterally for the right leg model); finally, the X-axis is perpendicular to the Y-axis and the Z-axis, pointing anteriorly. The origin of the tibial reference frame (t_{RF}) is located in the tibia at the midpoint of the transepicondylar markers. The axes of the t_{RF} are defined parallel to the f_{RF} in the anatomical position (i.e. with knee in full extension).

In the generic OpenSim model, the flexion-extension knee axis is defined about an axis through the epicondyles (TEA) (Figure 3.1A). In other words, the knee joint reference frames coincide with respectively the f_{RF} and t_{RF} and, therefore, the knee joint flexion axis is parallel to the Z-axis of both f_{RF} and t_{RF}. The position of the TEA in the f_{RF} depends on the knee flexion angle and is modeled as described by Yamaguchi *et al.* (1989). An additional rotational DoF about an axis parallel to the X-axis of f_{RF} was added to allow knee abduction-adduction (ab-adduction) motion.

The SARA algorithm (Ehrig *et al*., 2007) was selected (see Appendix A - Part A.1) to calculate the FAR, i.e. the averaged orientation and position of the knee flexion-extension axis throughout the motion in both the f_{RF} and t_{RF}, based on the coordinates of four markers on the thigh and four on the shank. The knee joint centre (KJC) is defined as the intersection of the FAR and the XY-plane of, respectively, the f_{RF} and t_{RF}. The orientation of the ab-adduction axis was then defined as the cross product of a unit vector pointing from the HJC to the KJC and the FAR. Hence, the ab-adduction axis is perpendicular to the flexion-extension axis and the plane in which the flexion-extension axis and the HJC lay. To include the FAR in the OpenSim model, the joint axis definition relative to the f_{RF} and t_{RF} was changed in each scaled model. To implement the FAR with respect to the f_{RF}, the knee joint reference frame with respect to the f_{RF} was redefined such that corresponds to the calculated location and orientation of the functional knee joint axis in the f_{RF}. To implement the functional axis with respect to the t_{RF}, the t_{RF} was adapted such that its origin coincides with the functional KJC and the Z- and X- axes of the t_{RF} coincide with respectively the knee flexion-extension and ab-adduction axes. To implement this change in segment reference frame, the locations of the tibia markers with respect to the t_{RF} were adapted. Furthermore, the location of the ankle joint with respect to the tibia was also adapted such that the position and orientation of the ankle joint with respect to the markers was preserved. Therefore, the knee joint reference frame expressed in tibia still coincides with the t_{RF} (Figure 3.1B).

Several characteristics of the motion used to calibrate the FAR, such as number of frames, minimum and maximum flexion angles, range of motion, movement scenario or type of motion, may influence the results obtained from the selected functional calibration method. Therefore, FARs were calculated in the control group based on five different motions assessing the effect of specific motion characteristics as potential confounding factors (Appendix A - Part A.2): stance phase of gait motion, stance phase of step-up motion and sit-to-stand-to-sit motion used as weight-bearing motions; and swing phase of step-up-and-over motion and dynamic motion used as non-weight bearing motions. Based on these results, FARs were calculated based on weight-bearing (stance phase of step-up motion) and non-weight-bearing (swing phase of step-up-and-over motion) motions for subjects with knee OA.

Data analysis

Data was processed according to a standard OpenSim 3.0 workflow (Delp *et al*., 2007): First, the generic model was scaled based on the marker positions during the static trial and the subject's body mass. For the models with FAR, the calculated weight-bearing FAR (wFAR) and non-weight-bearing FAR (nwFAR) were implemented into the scaled model. Joint angles and moments (normalized to body weight and height (%BW*Ht)) were calculated during gait using inverse kinematics and inverse dynamics and 3 to 6 trails were averaged for each limb.

Peak KAM during the first and second half of the stance phase of gait were determined for all models and groups. The ab-adduction angles at the instant of peak knee flexion during swing were calculated for the three groups.

Statistical analysis

To assess the effect of AoRs on kinematics and KAM, paired *t-test* (SPSS Inc., v17.0) evaluated the significance ($p < 0.05$) of the differences in ab-adduction angles at peak knee flexion angle during swing and in peak KAMs during stance between the TEA models and the two FAR models, for the three groups. The agreement between results obtained from TEAs and FARs were assessed by Bland-Altman plots (Bland and Altman, 1986) that evaluate a bias between the mean differences and it is significant if the line of equality was not within their confidence interval. Furthermore, Bland-

Altman plots estimate an agreement interval, within which 95% of the differences of the second method, compared to the first one, falls.

To assess differences in peak KAMs between the three groups using the same method to calculate the AoR, significance ($p < 0.05$) was evaluated using one-way analysis of variance (ANOVA) with Gabriel *post hoc* test.

The orientations of the ab-adduction rotation axis, expressed in the f_{RF}, between the wFAR and nwFAR models were compared using Wilcoxon matched-pair test ($p < 0.05$). The Figure A.3 (Appendix A - Part A.3) presents an example showing the difference in the frontal plane orientation observed between wFAR and nwFAR models.

3.3 Results

The knee flexion-extension and adduction-abduction angles during the stance phase for the three models are presented in Figure 3.2. While sagittal plane angles were similar between models, frontal plane angles were different with higher abduction angles for TEA models and higher adduction angles for FAR models. Higher inter-subject variation was observed in patients with established OA.

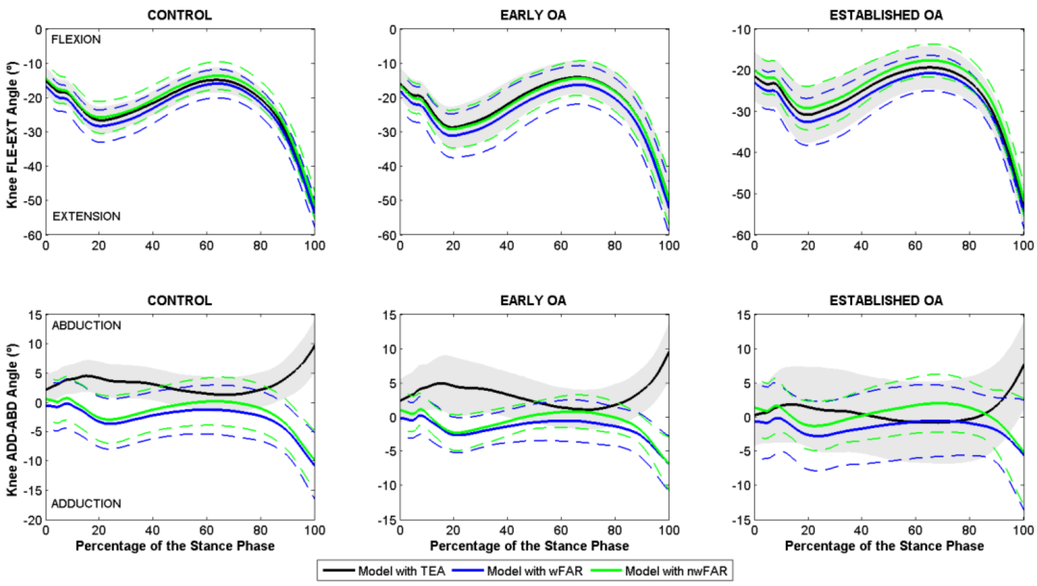

Figure 3. 2 - Knee flexion-extension (FLEX-EXT) and adduction-abduction (ADD-ABD) angles for the TEA (solid black line), FAR using a weight-bearing motion (solid green line) and FAR using a non-weight-bearing motion (solid blue line). The grey shaded area and the areas between the dashed lines indicate the standard deviation.

In the frontal plane, abduction angles at the instant of peak knee flexion in swing were 19º for the control and early OA groups, and 16º for the established OA group using the TEA models (Figure 3.2 and Table 3.1). Adduction angles at the instant of peak knee flexion in swing were 8º for the control and early OA groups, and 6º for the established OA group using the FAR models. Hence, using FAR instead of TEA significantly reduced the cross-talk. For the established OA group, there were small but significant differences in the knee abduction angle at maximum knee flexion between the model with nFAR (6.8º) and the model with nwFAR (6.2º), despite the large variation observed. The difference in the kinematics due to the use of TEA or FAR resulted in differences in KAM (Figure 3.3).

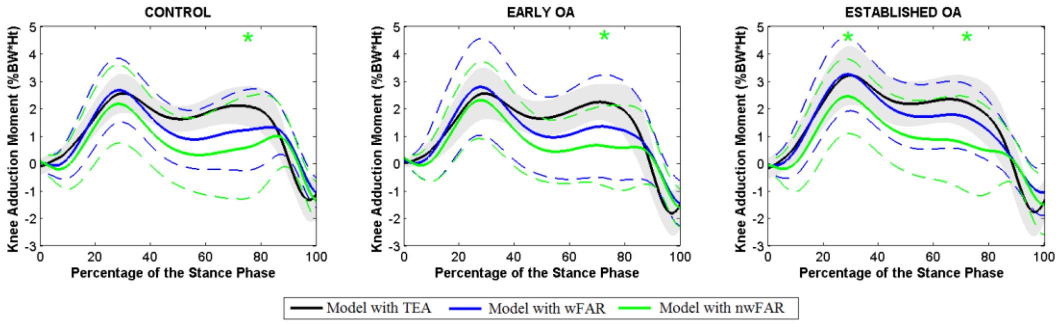

Figure 3. 3 - Mean knee adduction moments for the TEA (solid black line), FAR using a weight-bearing motion (solid green line) and FAR using a non-weight-bearing motion (solid blue line). The grey shaded area and the areas between the dashed lines indicate the standard deviation. * indicates the significant differences ($p < 0.05$) between TEA and nwFAR.

The peak KAMs were not significantly different between the models with TEA and those with wFAR (Figure 3.3). However, when models with TEA were compared to those with nwFAR, the second peak KAM was significantly reduced in all groups. Only in subjects with established OA both peak KAMs were significantly reduced in the nwFAR models when either compared to TEA models or wFAR models (Table 3.1).

Similar results were obtained from the Bland and Altman plots (Appendix A - Part A.4), for which significant bias was only found when TEA models were compared to nwFAR models, at the second peak for the control and early OA groups and in both first and second peaks for the established OA group. There was no bias between TEA and wFAR models.

Table 3. 1 - Average first and second peak values of KAM and abduction-adduction angles at the maximum flexion (during the swing phase of gait) calculated using a model with TEA (TEA) and the model with weight-bearing motion FAR (wFAR) and the model with non-weight-bearing motion FAR (nwFAR) for control, early OA and established OA groups.

			TEA	wFAR	nwFAR	***p*** **(TEA vs wFAR)**	***p*** **(TEA vs nwFAR)**	***p*** **(wFAR vs nwFAR)**
CO	**KAM**	**P1**	2.59±0.69	2.70±1.17	2.20±1.42	*0.722*	*0.220*	*0.130*
		P2	2.21±0.71	1.59±1.18	1.31±1.33*	*0.054*	***0.007***	*0.322*
EA	**KAM**	**P1**	2.59±0.90	2.83±1.77	2.33±1.41	*0.610*	*0.410*	*0.168*
		P2	2.40±0.67	1.70±1.49	1.22±1.15*	*0.115*	***0.001***	*0.169*
ES	**KAM**	**P1**	3.23±1.06	3.27±1.34	2.47±1.37*	*0.886*	***0.035***	***0.004***
		P2	2.40±0.87	1.85±1.20	1.15±1.37*	*0.098*	***0.002***	***0.007***
CO	**Abd-Add (º)**		-19.0±4.9	8.0±6.3	7.8±5.5	***0.000***	***0.000***	0.474
EA	**Abd-Add (º)**		-19.3±4.9	8.5±4.4	8.4±4.6	***0.000***	***0.000***	0.549
ES	**Abd-Add (º)**		-16.2±6.3	6.8±8.5	6.2±7.6	***0.000***	***0.000***	***0.011***

KAM expressed as mean ± SD (%BW*Ht), where SD is standard deviation.
P1 and P2 correspond, respectively, to first and second peak values.
CO, EA and ES correspond, respectively, to control, early OA and established OA groups.
Abd-Add corresponds to the abduction-adduction angle at the time instant of the peak flexion angle during the swing phase of gait and it is expressed in angles, in which positive values correspond to adduction angles and negative to abduction angles.
* It indicates a significant difference ($p < 0.05$) between TEA model and the respective FAR model.
Shaded gray indicates a significant difference ($p < 0.05$) between the wFAR and nwFAR models.

The significant differences in the first peak KAM between the three groups which was observed when using TEA ($p = 0.038$), were no longer present when using either FAR (Table 3.1 and Figure 3.4).

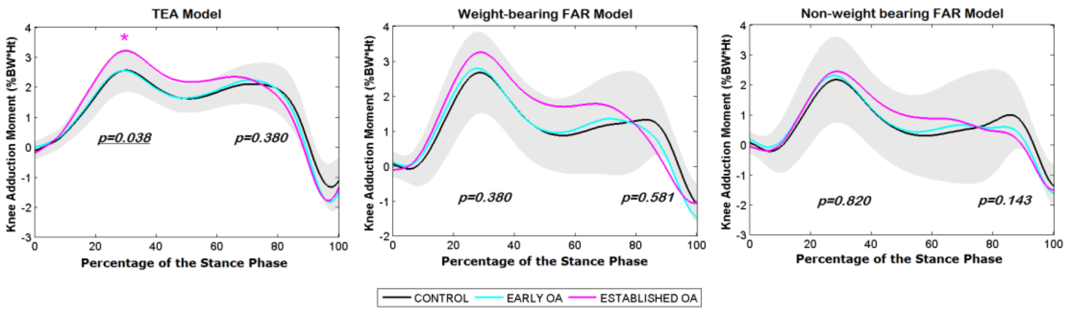

Figure 3. 4 - Mean KAM during stance phase of the gait cycle for the 3 groups using TEA model (left), weight-bearing FAR model (middle) and non-weight-bearing FAR model (right). * indicates the significant differences between groups.

Significant differences in the orientation of the ab-adduction axis were found between wFAR and nwFAR models in the established OA group (Table A.5 – Appendix A - Part A.3). Patients with established knee OA showed significantly increased adduction orientation in the wFAR models compared to the nwFAR models. Furthermore, a more detailed analysis showed that the use of wFAR generated 21 legs in adduction orientation with respect to the f_{RF} while the use of nwFAR generated only 15 (out of 33 legs) for patients with established OA.

3.4 Discussion

Several studies (Andriacchi, 1994; Fregly *et al*., 2007; Mundermann *et al*., 2008; Hurwitz *et al*., 2000; Guo *et al*., 2007; Miyazaki *et al*., 2002; Baliunas *et al*., 2002; Lewek *et al*., 2004) used the KAM as an indirect measure of medial compartment loading in patients with knee OA during functional activities. However, different methods (anatomical versus functional) to calculate the knee AoR have different sensitivities to marker errors. Since the accuracy of KAM is known to depend on the definition of the AoR in the knee joint, the effects of using anatomical (TEA) versus motion based (FAR) axes on the frontal plane external moments during walking were investigated in this study.

Our findings show that the use of a FAR effectively corrects the high abduction angles at peak knee flexion during gait obtained with TEA models (Figure 3.2, Table 3.1), confirming the results of previous studies (Schwartz *et al*., 2004). By using a FAR, frontal plane range of motion was reduced even presenting a reversal of the abduction motion, in both stance and swing phase. Excessive abduction angles during gait, especially those coinciding with peak knee flexion during the swing phase, have been shown to result from cross-talk (Baudet *et al*., 2014; Passmore and Sangeux, 2016). Therefore, our results suggest that the use of FAR may be beneficial in reducing cross-talk effect, which resulted from marker misplacement, observed in the present study. In addition, FAR models result in knee adduction during most of the gait cycle reaching the maximum knee adduction angles during the swing phase in agreement with previous literature (Kadaba *et al*., 1990; Desloovere *et al*., 2010; Scheys *et al*., 2013).

First peak KAM was reduced when using FAR compared to TEA (Figure 3.2), up to a point where significant differences between the different groups were no longer present (Figure 3.3). This was especially pronounced in established OA, where the first and second peak KAMs calculated using nwFAR were significantly lower compared to the TEA models and to the wFAR models. The differences in the KAM, due to the differences in FAR calculated in weight-bearing and non-weight-bearing is relevant as tibiofemoral kinematics is known to be load-dependent (Markolf *et al.*, 1981; Dyrby and Andriacchi, 2004), and therefore the position and orientation of a functionally identified AoR are likely to differ between activities with variable loading conditions. Subjects with established OA**,** presented FAR that were more adduction oriented with respect to the f_{RF} during weight-bearing compared to non-weight-bearing conditions as reflected in the significant differences in the orientation around the ab-adduction axis between wFAR and nwFAR models.

This finding suggests that in patients presenting structural degeneration, the FAR orientation calculated in weight-bearing is indicative of a more adducted joint alignment as reflected in the more adducted orientation of the axis in the f_{RF} compared to healthy subjects. Therefore, the higher adduction orientation found in wFAR models better reflects load-dependent knee kinematics, which has been shown to be especially important for patients with end-stage knee OA (Dyrby and Andriacchi, 2004).

Our results have to be interpreted in view of certain methodological limitations. First, although the functional methods present the advantage of being less dependent on the marker placement than the TEA axis, these methods are still sensitive not only to the type of the calibration motion, as demonstrated, but also to soft tissue artefacts, i.e., the relative movement between markers and bone. However, since there was no significant difference in BMI between the groups, soft tissue artifacts may have affected the three groups similarly and, therefore, differences between groups did not likely result from this error. Second, only the knee joint axis was determined based on functional motions. However, the definition of the other joints influences knee kinematics as well (Reinbolt *et al*., 2005), especially the ankle joint, for which only one DoF was considered. Even though, marker errors after inverse kinematics were similar for TEA and FAR models and hence the introduction of a functional axis did not negatively affect the fit with the experimental data, which might have been the case given the coupling between the different joints. Third, the knee internal-external rotation was not included due to the marker set used during the data collection, which was found to be closely aligned with the longitudinal rotational axis. Therefore, any wobbling of the marker would inflate into a large change in the internal-external rotation. This is not an issue for the ab-adduction motion since the markers are further away from the abduction axis.

3.5 Conclusions

In conclusion, excessive KAM was or was not confirmed in subjects with established OA, depending on the AoR used to calculate the KAM. Therefore, this study underlines the sensitivity of the KAM to knee axis definition. In many clinical studies, the definition of the knee AoR is considered a methodological detail that is often not reported. However, our findings suggest that differences in axis definitions between studies may explain the variability in reported relation between KAM and OA progression and should be considered with care when comparing different study outcomes. In studies on knee OA, the use of weight-bearing motions should be considered for the calculation of FAR to better account for the load-dependent knee instability.

Author contributions

All authors take responsibility for the integrity of the work as a whole, including data and accuracy of the analysis. Conception: S. Meireles, F. De Groote, S. Van Rossom, and I. Jonkers. Design: S. Verschueren and I. Jonkers. All the authors contributed to the **a**nalysis and interpretation of the data, drafting of the article and final approval of the article.

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Competing interests

All authors declare no conflict of interest.

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Chapter 4

Medial knee loading is altered in subjects with early OA during gait but not during step-up-and-over task.

Submitted as

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4.1 Introduction

Osteoarthritis (OA) is a chronic degenerative and multifactorial (Lories and Luyten, 2011; Andriacchi *et al.*, 2004) joint disease that most frequently affects the knee (Buckwalter and Martin, 2006) causing pain and functional disability. To date, there are no therapeutic interventions that overcome or effectively delay the progression of this disease and symptoms can only be managed (McAllindon *et al.*, 2014). Identifying the risk factors associated with early stages of OA is imperative to classify patients at high risk to develop established knee OA and better assess effective treatments to protect joint integrity before major structural damage occurs.

Although the cause of OA is still not completely understood, biomechanical factors are known to play an important role (Nike and Salter, 2007; Radin and Rose, 1986). Aberrant knee joint loading has been identified as a factor affecting the progression of knee OA (Fregly *et al.*, 2007; Mundermann *et al.*, 2008; Hurwitz *et al.*, 2000). External joint moments can be readily calculated from motion analysis data and thus have been proposed to identify characteristics of OA patients. Reduced external knee flexion moment (KFM), the external knee joint moment in the sagittal plane, is commonly reported for OA patients as a consequence of quadriceps weakness (Landry *et al.*, 2007; Roos *et al.,* 2011; Hurley, 1998; Slemenda *et al.*, 1997). Increased knee adduction moment (KAM), the external knee joint moment in the frontal plane, has been used as a parameter reflecting increased medial tibiofemoral loading (Andriacchi, 1994; Miyazaki *et al.,* 2002; Baliunas *et al.,* 2002; Meyer *et al., 2013;* Walter *et al.,* 2010; Kutzner *et al.,* 2013; Kumar *et al.,* 2013; Baert *et al.,* 2013) and associated with the presence of medial knee OA (Sharma *et al.,* 1998). However, some studies in patients with early stages of knee OA suggest that altered KAM and KFM are not risk factors in the initial development of knee OA (Kumar *et al.,* 2013; Baert *et al.,* 2013; Duffell *et al.,* 2014). Only a few studies examined the external knee rotation moment (KRM), the external moment in transverse plane, for patients with knee OA (Landry *et al.,* 2007; Gok *et al.,* 2002; Wilson *et al.,* 2013; Harding *et al.,* 2012; Kang *et al.,* 2014), and they report contradictory findings of altered KRM in patients with OA compared to healthy subjects. For KRM, no comparison between early and established OA patients is available to date. Consequently, the ability of external joint moments to identify the onset of OA is still under debate (Baert *et al.,* 2013).

Knee joint moments depend only on kinematics and external forces and, therefore, do not account for muscle forces. Consequently, a reduction in peak KAMs does not necessarily indicates a reduction in medial contact load (Walter *et al.,* 2010; Meireles *et al*., 2016). On the other hand, knee contact force (KCF), calculated using musculoskeletal modeling in combination with simulations of motion, directly reflect cartilage loading by accounting for muscle and ligament forces.

A previous study from our group showed that in early stages of knee OA, overall KCFs were not different from those in control subjects (Meireles *et al*., 2016), but were increased in subjects with established OA. By differentiating the loading on the medial and lateral compartment, Kumar et al. (Kumar *et al.,* 2013) found increased medial KCF in patients with established OA (with Kellgren-Lawrence score (K&L) ≥ 2) compared to healthy subjects. Marouane *et al.* (2016), have recently reported KCFs and their respective locations during the stance phase in both healthy subjects and subjects with established knee OA (K&L = 3 or 4) aiming to compare various approaches to compute the KCF locations in both groups but no comparison was done between the two groups. Therefore, to date no information on the medio-lateral load distribution in terms of knee contact forces and/or alterations in contact locations of loading in the joint are available in early OA patients. However, based on gait characteristics of a subject following anterior cruciate ligament (ACL) injury, alterations in cartilage surface contact location have been suggested to occur during gait and associated to the high incidence of medial knee OA after ACL injury (Andriacchi *et al*., 2006). Interestingly, advances in musculoskeletal modeling now enable evaluation of the pressure distribution in the joint and therefore can provide insight into the load-bearing regions of the knee joint (Smith *et al.,* 2016; Koo *et al.,* 2003). As such, shifts in contact location during weight-bearing activities can be evaluated, an action mechanism often suggested to contribute to the onset of OA (Andriacchi *et al*., 2004).

Most studies in literature have focused on knee loading during gait as a biomarker for OA onset and progression. However, subjects with knee OA initially present pain complaints in more demanding tasks, specifically weight-bearing activities that involve large knee flexion (Hensor *et al*., 2015). But only a few studies have reported joint moments (Hensor *et al*., 2015; Guo et al., 2007; Asay *et al.*, 2009; Kaufman et al., 2001; Igawa and Katsuhira, 2014) and muscle activations (Liikavaino, 2010) during stair negotiation in patients with advanced stages of knee OA. Studies have shown altered knee loading in stair negotiation, such as reduced KFM (Hensor *et al*., 2015; Igawa and Katsuhira, 2014) and indications of lower KAM during stair ascent and descent (Asay *et al.*, 2009) in patients with knee OA compared to healthy subjects. So far, compartmental joint loading in terms of KCFs has not been described in patients with early or established knee OA during higher demanding tasks. However, these metrics are extremely relevant, as demanding movements might exemplify mechanical alterations earlier and therefore may be more sensitive in identifying early OA, enabling earlier screening and treatment.

The first aim of this study is to evaluate the magnitude of knee joint loading (as measured with KCFs) during gait in patients with early knee OA, and those with established knee OA compared to healthy subjects, as well as the maximum contact pressures and their respective locations. We hypothesize that these parameters are more sensitive in detecting early changes in knee joint loading in early OA subjects, prior to the onset of structural degeneration. Secondly, this study evaluates knee joint loading during step-up-and-over task in early OA subjects. We hypothesize that this higher demanding activity may already cause larger alteration in the medial compartment loading, present prior to alterations during gait and, therefore, may be able to discriminate patients with early knee OA from healthy subjects.

4.2 Methods

Participants

Fifty-three participants (all women, mean age of 64.8±7.5 years) were recruited for this study. Subjects were separated into three groups: asymptomatic healthy subjects (*n* = 19) as control; patients with symptomatic early medial knee OA based on a novel classification criteria of Luyten *et al.* (2012) using Magnetic Resonance Imaging (MRI) (*n* = 18), and patients with symptomatic established medial knee OA based on the American College of Rheumatology (Altman et al., 1986) classification criteria (*n* = 16). More details about patient classification can be found in Meireles *et al.* (2016). All procedures were approved by the local ethics committee of Biomedical Science, KU Leuven, Belgium. Written informed consent was obtained from each subject.

Subject characteristics are listed in Table 4.1. Knee pain was assessed through the Knee Injury and Osteoarthritis Outcome Score (KOOS) (Dutch version (De Groote *et al*., 2008). Knee joint alignment in the frontal plane was measured by a single experienced observer on full-leg, anterior-posterior, weight-bearing radiographs of the lower limbs (Oldelft, Triathlon, Agfa ADC M Compact Plus) (Sharma *et al*., 2001).

For healthy subjects, both legs were analyzed. For symptomatic patients with unilateral knee OA, only data of the affected knee were analyzed. For those with bilateral knee OA, both legs were analyzed except if the less involved side presented with a K&L score ≤ 2 (Figure 4.1 and Table 4.1) for the established OA group.

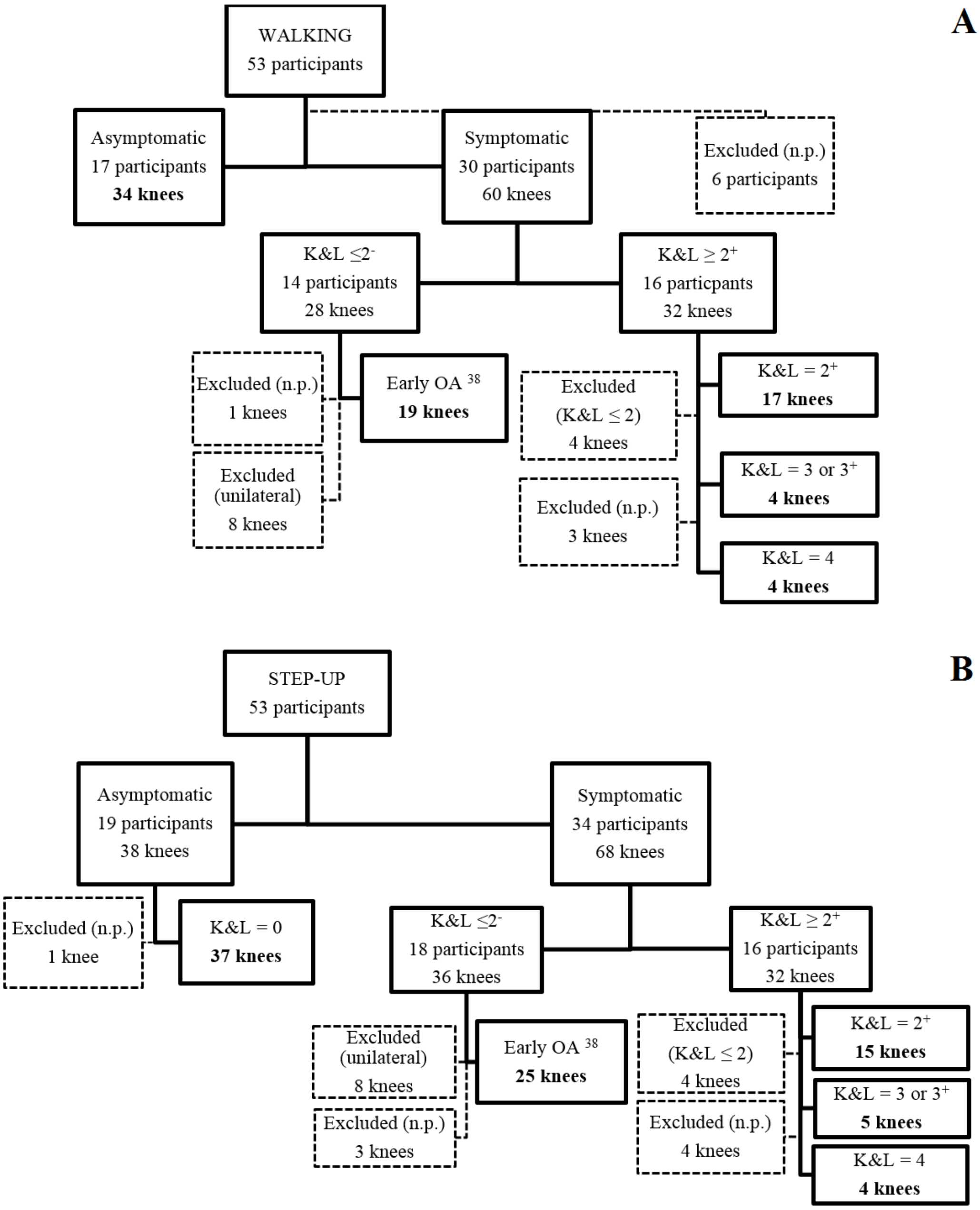

Figure 4. 1 - Flow charts of the limbs selection for gait (A) and step-up-and–over (B). The final number of the analyzed limbs are indicated in bold. During gait, 11%, 50% and 7% of the total knees diagnosed with early OA presented K&L of 0, 1 and 2, respectively. During step-up-and-over, 17%, 47% and 6% of the total knees diagnosed with early OA presented K&L of 0, 1 and 2, respectively. Numerical problems are indicated as n.p.

All recruited subjects performed gait and step-up-and-over tasks. However, due to numerical problems during the simulation, six subjects were excluded from the gait analysis. More details about the participants' selection and the total number of limbs included in each group are presented in Figure 4.1.

Motion analysis

An active 3D motion analysis system (Krypton, Metris) recorded the 3D position of 27 LEDs at a sampling frequency of 100 Hz placed according to an extended Helen Hayes protocol (consisting of 5 technical clusters and 12 anatomical landmarks). A force plate (Bertec Corporation, USA) measured ground reaction forces sampled at 1000 Hz. Marker data were labeled and smoothed using a spline routine (Woltring, 1986) in Matlab R2010b Version 7.11 (Mathworks, inc.).

Gait analysis consisted of level walking along a 10 m walkway at self-selected speed with the force plate embedded in the middle of the walkway. The subjects were required to perform 6 trials for each leg.

Step-up-and–over analysis consisted of stepping onto a 20-cm-high step with one leg (stepping leg), while stepping over with the other leg (trailing leg) making contact on the other side of the step (Figure 4.2). The force plate was embedded in the ground under the step. The subjects performed a total of 3 trials for each leg.

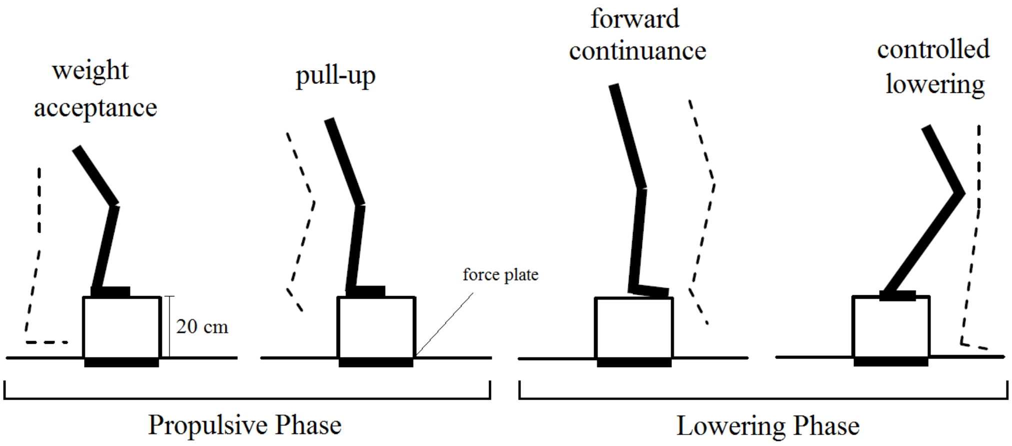

Figure 4. 2 - A schematic illustrating the step-up-and-over task (adapted from Reid (2010)). The stepping leg (bold) is the leg considered for further analysis.

Barefoot condition was chosen in order to optimize standardization since variation in footwear would influence lower limb loads (Shakoor and Block, 2006).

Musculoskeletal Model

A multi-body knee model (Figure 4.3) with 6 degrees of freedom (DoF) for the tibiofemoral and patellofemoral joints was used (Lenhart *et al*., 2015). Fourteen ligaments were represented by bundles of nonlinear elastic springs. A contact moedel based on an elastic foundation formulation (Bei and Fregly, 2004) was included in the knee model. The knee model was integrated into an existing lower extremity musculoskeletal model (Arnold *et al.,* 2010), which included 44 musculotendon units crossing the hip, knee and ankle joints.

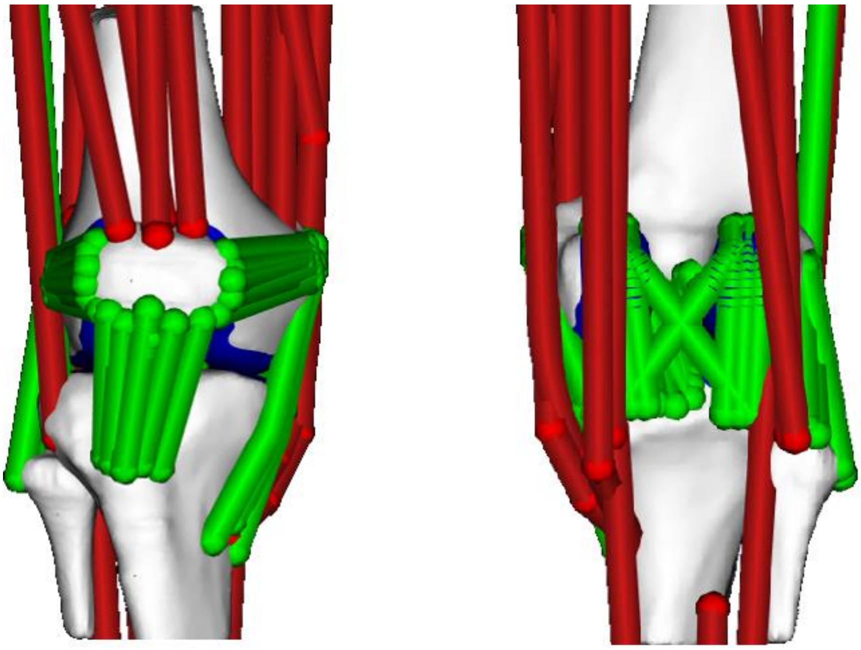

Figure 4. 3 - Multibody 12 degree of freedom knee model including ligaments and an elastic foundation contact model (Lenhart et al., 2015).

The lower extremity model was scaled to subject-specific segment lengths as determined in a static calibration trial. The joint angles were computed using an inverse kinematics algorithm. The concurrent optimization of muscle activations and kinematics (COMAK) algorithm (Smith *et al*., 2016; Lenhart *et al*., 2015), was used to compute the secondary tibiofemoral and patellofemoral kinematics, muscle and ligament forces, and contact forces by minimizing the muscle volume weighted sum of squared muscle activations plus the net knee contact energy. The elastic foundation model (Bei and Fregly, 2004) calculated the tibiofemoral contact pressures and their respective locations over the stance phase of gait and step-up-and-over. Subsequently, an inverse dynamics algorithm computed the external joint moments: KFM, KAM and KRM.

Calculated KCFs were normalized to body weight (BW) and moments were normalized to the product of body weight and height (BW×Ht). All data were time normalized to the stance phase (i.e. from initial contact to toe off).

Data analysis

During gait, KCF, moments and angles throughout the stance phase were averaged over all trials for each leg. The peaks during the first and second half of the stance phase were determined for the total KCF, medial KCF, and lateral KCF, KFM and KRM. The minimum values during the single support (SS) phase were determined for KCF and KFM. For the KAM, only the first peak during early stance phase, corresponding to the highest peak of the stance, was calculated. Although two peak KAMs have been reported for healthy subjects and patients at early stages of OA, patients with advanced medial knee OA frequently present one peak during early stance and, therefore, a minimum value and a second peak was not always clear (Baert *et al*., 2013; Butler *et al*., 2011; Kito *et al*., 2010; Baliunas *et al*., 2002; Astephen *et al*., 2008). A similar trend was found in our study, in which some patients with established knee OA did not show a distinct second peak.

During step-up-and-over, KCF, moments and angles of the stepping leg were averaged across trials throughout the stance phase. The maximal total KCF, lateral KCF, KFM and KAM during the first and second half of the stance phase and the minimum values during the SS phase were determined. Also, the highest peak medial KCF during the stance phase was compared between groups. Due to the high variation in the individual KRM pattern observed in patients with established OA during this task, maximum values of KRM were not calculated and only the average curve is presented.

Furthermore, maximum contact pressures in the medial compartment and the locations of the centers of contact pressure (CoPs) were assessed at the instant of peak medial KCF for the three groups.

Statistical analysis

One-way analysis of variance (ANOVA), performed with SPSS Inc., v17.0, evaluated whether differences in peaks and minimum moments, peak KCFs, maximum contact pressures and CoP locations were significantly different ($p \leq 0.05$) between the three groups. As sample sizes were slightly different, Gabriel *post hoc* test was used to assess whether the differences between groups were significant.

The effect size (Cohen's *f*) on these ANOVA tests were evaluated using G*Power 3.1.9.2 (Faul *et al*., 2007), based on the assumption of less than 5% Type I error. The effect size (*d*) for the *F*-test ANOVA were considered small for $f = 0.10$, medium for $f = 0.25$ and large for $f = 0.40$ (Cohen, 1988).

4.3 Results

Subject characteristics

Age, body mass, height, and speed for gait and step-up-and–over did not differ significantly between the three groups (Table 4.1). Both OA groups reported significantly greater knee pain (p < 0.001) than controls, but no difference was found between the two groups of OA patients. Patients with established OA presented significantly higher varus alignment compared to controls in both *gait* and *step-up-and-over* (p = 0.010 and p = 0.003, respectively).

Table 4. 1 - Characteristics of the groups: control (C0), early OA (EA) and established OA (ES).

	Task	**Control**	**Early OA**	**Established OA**	***p***	***p* (C0-EA)**	***p* (C0-ES)**	***p* (EA-ES)**
No. of subjects	Gait	17	14 (6uni+8bi)	16 (16bi)	-	-	-	-
	Step	19	18 (8uni+19bi)	16 (16bi)	-	-	-	-
Age, *years*	Gait	64.2±9.0	63.3±7.7	67.2±6.7	0.362	0.985	0.619	0.449
	Step	64.3±8.5	63.3±7.0	67.2±6.7	0.305	0.965	0.598	0.351
Body mass, *kg*	Gait	64.0±7.9	69.7±16.6	73.3±11.9	0.103	0.494	0.102	0.809
	Step	64.6±7.7	70.0±15.5	73.3±12.0	0.103	0.440	0.109	0.813
Height, *m*	Gait	1.61±0.1	1.62±0.1	1.61±0.1	0.828	0.971	0.993	0.903
	Step	1.62±0.1	1.62±0.1	1.61±0.1	0.837	0.994	0.974	0.910
KOOS pain score	Gait	100±0.0	82.9±17.7	73.3±19.4	**0.000**	**0.005**	**0.000**	0.203
	Step	100±0.0	84.4±15.4	73.4±19.4	**0.000**	**0.004**	**0.000**	0.075
Speed, *m/s*	Gait	1.21±0.2	1.26±0.2	1.20±0.2	0.426	0.623	0.992	0.524
	Step	0.53±0.1	0.55±0.1	0.57±0.1	0.311	0.663	0.371	0.966
Knee Alignment in the frontal plane ^{o}	Gait	0.50±2.3 (24)	1.46±3.4 (15)	3.66±3.5 (13)	**0.014**	0.701	**0.010**	0.164
	Step	0.45±2.5 (26)	1.14±3.2 (18)	4.03±3.5 (12)	**0.004**	0.831	**0.003**	**0.034**

Values are the mean ± Standard Deviation (SD). ANOVA with Gabriel *post hoc* test. Significant difference p < 0.05 are indicated in bold.

For the knee alignment, positive values indicate varus (adduction) alignment and negative values indicate valgus (abduction) alignment.
Uni corresponds to the number of patients with unilateral OA and *bi* to those with bilateral OA.

Knee joint loading during gait

Only patients with established knee OA showed significantly higher peak and minimum total KCFs (Figure 4.4), when compared to controls ($p = 0.012$ and $p = 0.013$ during both first and second peak and $p < 0.0001$ during SS). No significant difference in total KCF was found between early OA and control subjects.

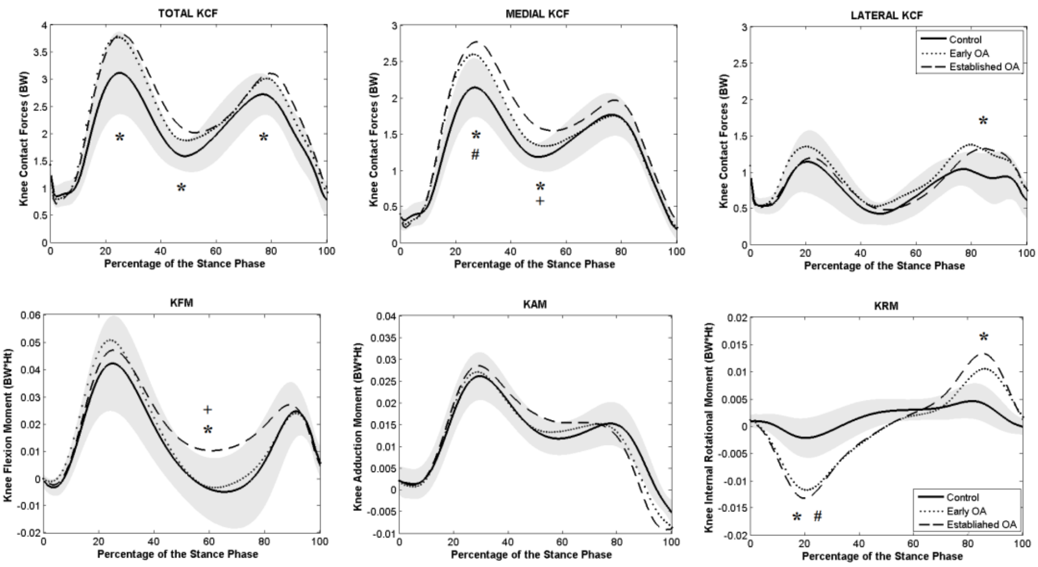

Figure 4. 4 - Averaged total, medial and lateral knee contact forces (above), and knee moments in the sagittal, frontal and transversal planes (below) during stance phase of gait. The gray shaded area corresponds to the standard deviation of the control group. * indicates a significant difference between established OA and control group. # indicates a significant difference between early OA and control group. + indicates a significant difference in the evaluated values between the early and established OA.

Lateral compartment KCFs were higher in both OA groups during second part of stance, however, the increase was only significant for the established knee OA group (p = 0.009) compared to healthy subjects (Table B.1 – Appendix B – Part B.2).

Both patient groups presented higher peak medial KCF compared to controls (p = 0.001, established OA and p = 0.048, early OA). However, only the established OA presented significantly higher medial KCF during the midstance when compared to the other two groups.

In Figure 4.5, the averaged contact pressure distributions on tibial and femoral plateaus at the time instant of the first peak medial KCF are presented for the three groups. At this time instant, the tibia was significantly more externally rotated for both OA groups (rotation angle of -7.4º±14.0º and -14.6º±14.3º, respectively, early and established OA) compared to the controls (rotation angle of +0.3º±5.1º) (Figure B.1 and Table B.1 – Appendix B, respectively, Part B.1 and Part B.2). Maximum contact pressure was significantly higher for subjects with established OA compared to control and early OA groups. In subjects with early knee OA, the medial compartment CoP at the instant of the first peak medial KCF significantly shifted from central (as seen in the control subjects) to a more posterior region, and to a more postero-lateral region in subjects with established OA.

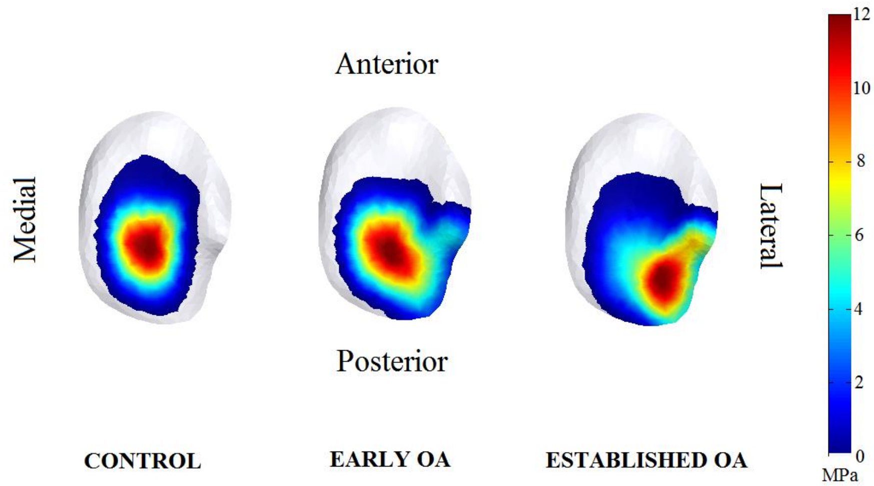

Figure 4. 5 - Averaged contact pressure distributions on the articular surfaces of medial tibial plateau at the time instant of the first peak medial KCF. Results are presented for the healthy group (on the left), the early knee OA group (in the middle), and the established knee OA group (on the right).

No significant differences were found in peak KFM or KAM between the three groups. During SS, patients with established knee OA presented significantly higher KFM compared to control and early OA groups (Table B.1 – Appendix B – Part B.2). First peak KRM was significantly higher in early (0.015±0.013×BW*Ht, $p < 0.0001$) and established OA (0.015±0.014×BW*Ht, $p < 0.0001$) groups compared to healthy subjects (0.003±0.003×BW*Ht). Only established OA showed significantly higher second peak KRM (Figure 4.4).

For all reported significant differences, the effect size was large or medium to large ($f \geq 0.34$) and the statistical power ranged from acceptable (*power* ≥ 0.80) to very high (*power* ≥ 0.95) as presented in Table B.1 (Appendix B – Part B.2). Only for the second peak KRM a power lower than 0.80 was found.

Knee joint loading during step-up-and-over

No significant differences in KCF, either medial or lateral, were observed between the groups (Figure 4.6). Due to the high variability in terms of joint angles (Figure B.1), moments and contact forces (Table B.2 – Appendix B – Part B.2) between subjects during the step-up-and-over task, the effect sizes obtained were small to medium and statistical power did not achieve the acceptable minimum power. Therefore, the contact pressure data was not further analyzed.

Patients with established knee OA did present significantly lower first peak KFM compared to controls ($p = 0.038$) (Table B.2 – Appendix B – Part B.2). No significant differences were observed in terms of KAM between the three groups (Figure 4.6).

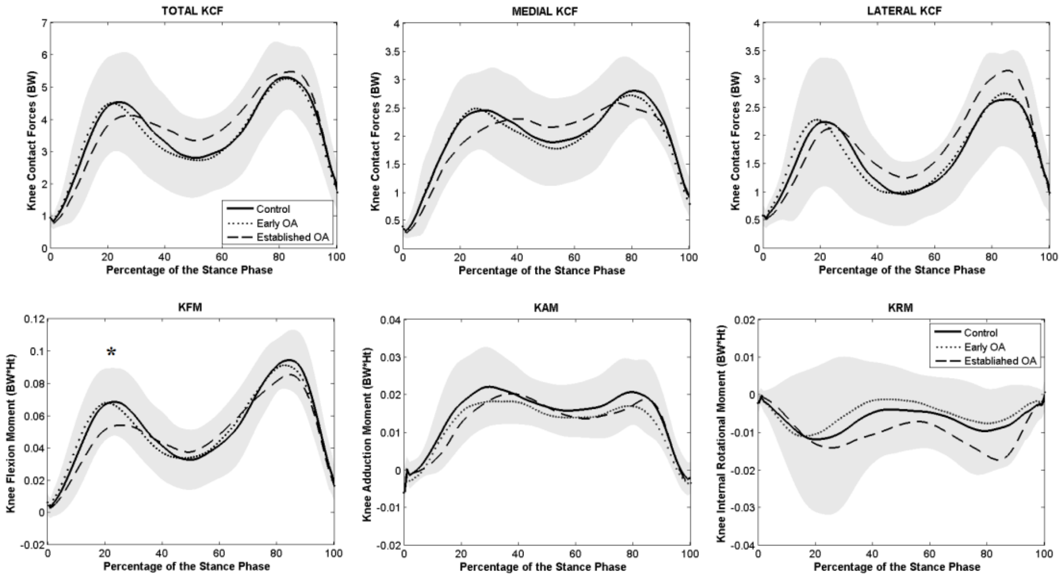

Figure 4. 6 - Averaged total, medial and lateral knee contact forces (above), and knee moments in the sagittal, frontal and transversal planes (below) during stance phase of step-up-and-over. The gray shaded area corresponds to the standard deviation of the control group. *indicates a significant difference between established OA and control group.

4.4 Discussion

This study investigated magnitude and location of knee loading during gait and step-up-and-over in subjects with early as well as established medial knee OA. We evaluated how loading changes, both contact forces and contact pressure distributions, in patients with early OA compared to healthy subjects and patients with established OA to see whether quantifiable changes in loading are already present in early OA.

Knee joint loading during gait

Whereas the first peak total KCF has shown to be almost significant, only the first peak medial KCF significantly has increased in patients with early OA compared to control subjects. Only patients with established OA presented significantly increased first and second peak total KCFs together with a significant first peak medial KCF. Likewise, although the maximum contact pressure increased in both groups of patients compared to controls, it was only significant in patients with established OA. This partially confirms our first hypothesis, in which medial KCF during *gait* showed to be sensitive in detecting early changes in the knee loading. Nevertheless, both groups of patients with knee OA showed a shifted CoP at the first peak medial KCF which, in combination with increased external rotation of the tibia during early stance, shows that patients with knee OA tend to load a more posterior (both groups) and lateral (established OA) cartilage region of the medial tibia plateau, which is not loaded in healthy subjects (Figure 4.4). This suggests that, although excessive loading is not revealed by the total KCF in the early phase of the disease, the medial-lateral forces distribution and pressure distribution are altered. Only when clear structural degeneration is present (KL>2), as in the established OA group, do changes in gait mechanics that result in excessive total knee loading occur. The abnormal transverse plane kinematics, particularly the increased of the external rotation in patients with OA shifted the normal load bearing contact to regions in the cartilage which are less predisposed for higher loads and therefore might influence the initiation of knee OA.

In regards to the external joint moments during gait, only peak KRMs were significantly different between patients with early knee OA and healthy subjects. Patients with established OA showed increased midstance KFM, but also no differences in peak KAM or KFM compared to the other two groups, confirming our previous study (Meireles *et al*., 2016). First peak KRM was increased in patients with knee OA compared to healthy subjects. For patients with established OA, the excessive rotation moments persisted during late stance. This confirms the study of Gok *et al.* (2002) and Wilson *et al.* (2013) who found higher rotation moment in patients with knee OA compared to healthy subjects.

The present study provides important insight into the altered medial loading magnitude and medial pressure location which were found to be already present in patients at early stages of medial knee OA, but was not revealed by the total contact force. With progression of structural degeneration, alterations in gait mechanics led to increased overall joint loading, affecting both the medial and lateral compartment. Therefore, medial KCF rather than KAM or total KCF during gait provides the most sensitive marker for early OA.

Knee joint loading during step-up-and-over

High variations in movement strategies between subjects, particularly in those having knee OA, were observed during step-up-and-over. Due to these high variations, the statistical power was low. Consequently, step-up-and-over does not generate large differences in kinematics and loading patterns, which might be due to the difficulty of standardizing the movement performance with respect to speed of movement. As a more demanding task, step-up-and-over seems to motivate subjects, particularly those with knee OA, to search more for alternative movement strategies to deal with and, therefore, generating elevated variations.

In contrast to our second hypothesis, no significant differences were observed in knee loading between patients with early knee OA and healthy subjects during step-up-and-over. However, most patients with established knee OA presented a different timing of the highest peak medial KCF compared with the other two groups. This difference in the loading pattern observed in patients with established OA needs further analysis.

Interestingly, during step-up-and-over, no significant differences in peak KAM were found between early OA and healthy subjects, or even between established OA and controls, although the high variation in the data indicates larger subject numbers may be necessary to effectively study this task. Nevertheless, patients with established knee OA showed reduced first peak KFM compared to the control group and also to the early knee OA group during the upward propulsive phase (step ascent). This finding is in line with previous studies in stair negotiation (Hurley, 1998; Slemenda *et al*., 1997; Kaufman *et al.,* 2001; O'Reilly *et al.*, 1998), in which patients with established knee OA also presented altered movement strategies in the sagittal plane.

Limitations of this study

These results have to be interpreted in view of some methodological limitations, as inherent to the model used (Lenhart *et al.,* 2015). We used a single generic knee model that was scaled to represent the anthropometry of the subjects instead of considering the subject-specific articular geometries, including those of the tibia plateau. The model does not account for OA induced changes in articular geometry, thickness and mechanical properties of the cartilage or changes in the ligaments. Therefore, the reported differences in contact forces and pressures only result from altered kinematic and kinetic behavior. As a result, it will not necessarily capture co-contraction patterns that have seen in patients with knee OA and may heighten loading (Hubley-Kozey *et al.,* 2009).

4.5 Conclusions

Altered knee joint loading and pressure location during gait were found to be already present in early OA, as confirmed in the elevated medial compartment contact forces, a shift in the center of pressure and elevated knee rotation moment. Our findings indicate that medial knee contact force predicted by a novel musculoskeletal simulation routine provides a more sensitive metric than the KAM used by previous researchers to identify early knee OA development prior to the onset of radiographic evidences. Excessive medial contact forces might be a risk factor for further progression.

Since the increased demand, required for performing step-up-and-over, caused patients to have a large variability in their approach to the task, against our expectations, it is not a great task to discriminate better loading profiles between patients with early knee OA from healthy subjects.

Author contributions

All authors take responsibility for the integrity of the work as a whole, including data and accuracy of the analysis. Conception: S. Meireles, M. Wesseling, C.R. Smith, D.G. Thelen, I. Jonkers. Design: S. Meireles, I. Jonkers, S. Verschueren. All the authors contributed to the analysis and interpretation of the data, drafting of the article and final approval of the article.

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Competing interests

All authors declare no conflict of interest.

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Chapter 5

Patients with medial knee osteoarthritis reduce medial knee contact forces by altering trunk kinematics, progression speed, and stepping strategy during stair ascent and descent

Submitted as

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5.1 Introduction

Stair negotiation and level walking are common activities of daily living. However, stair negotiation is biomechanically more challenging (Nadeau *et al.*, 2003), demanding a higher range of motion (RoM) in the lower extremity (Nadeau *et al.*, 1997), higher moments acting at the knee joint (Costigan *et al.,* 2002; Kaufman *et al.*, 2001; Andriacchi *et al.*, 1980) and, consequently, greater quadriceps demands compared to level walking. Thus, stair negotiation is particularly demanding for the elderly or subjects with knee osteoarthritis (OA) (Liikavainio *et al.*, 2010), who often face the first difficulties in daily task performance and pain complaints (Hensor *et al.,* 2015), particularly during stair descent (Salsich *et al*., 2001). However, stair negotiation has not been deeply explored in OA with most studies in the literature focusing on knee loading during level walking as a biomarker for OA onset and progression. Previous literature has shown reduced knee flexion moment (KFM) (Hensor *et al*., 2015; Igawa and Katsuhira, 2014; Kaufman *et al.*, 2001), non-conclusive findings in knee adduction moment (KAM) (Kaufman *et al.*, 2001; Linley *et al.*, 2010) and altered muscle activation patterns (Liikavainio *et al.*, 2010) in severe knee OA patients during stair negotiation. In addition, these patients have exhibited higher trunk flexion angles (Asay *et al.*, 2009; Andriacchi *et al.*, 1985) and hip flexion moments (Asay *et al.*, 2009; Hicks-Little *et al.*, 2011) than healthy subjects while ascending stairs (Asay *et al.*, 2009). These alterations observed in OA patients have been associated with a loss of quadriceps function (Hurley, 1998; Slemenda *et al.*, 1997) as these muscles provide extensor moments necessary to accelerate the upward propulsive phase occurring during the first part of stair ascent and to decelerate the lowering of the body during stair descent (Lu and Lu, 2006).

Generally, healthy and young individuals use a traditional step-over-step (SOS) motion pattern during stair negotiation, but OA patients frequently feel forced to adjust their stair gait due to knee pain, reduced RoM, muscle weakness, stiffness and instability complaint (Bhatia *et al.*, 2013; Liikivainio *et al.*, 2008). Therefore, they often adopt alternate walking patterns, such as increased handrail use, sideways motion, or a step-by-step (SBS) patterns (placing both feet on the same step) (Shiomi, 1994; Startzell *et al.*, 2000) and/or a significantly reduced speed (Kaufman *et al.*, 2001; Hicks-Little *et al.*, 2012). In healthy subjects, the SBS strategy has been demonstrated to require higher energy costs, lower efficiency, and an increased risk of falling than SOS (Shiomi, 1994; Reid *et al.*, 2007). However, significant reductions in KFM were found for the leading leg during SBS when compared to SOS while descending stairs in healthy subjects, and reduced anteroposterior force for SBS versus SOS either during stair ascent or descent (Reid *et al.*, 2007).

To date it is still unknown how these altered patterns observed in individuals with knee OA affect the compartmental knee contact force (KCF) as mainly kinematics and kinetics (Kaufman *et al.*, 2001; Asay *et al.*, 2009; Lessi *et al.*, 2012) have been explored, which do not provide direct measures of cartilage loading. Previous research has clearly shown that during level walking, the KCFs are not entirely determined by external moments, particularly in patients with established knee OA (Meireles *et al.*, 2016). To our knowledge, KCF calculated using musculoskeletal modeling that accounts for muscle and ligament forces in combination with simulations of motion, has never been used in individuals with knee OA during stair negotiation. Furthermore, the effectiveness of the observed speed reduction (Kaufman *et al.*, 2001; Hicks-Little *et al.*, 2012) and changes in stepping strategy in controlling knee joint loading during stair negotiation is unexplored.

The first objective of this study was to compare knee joint loading and trunk kinematics during stair ascent and descent in individuals with medial knee OA against healthy subjects during SOS at controlled speed. We hypothesize that OA patients present lower knee loading than healthy subjects trying to avoid pain. The second objective was to investigate the influence of stair negotiation strategy on knee joint loading magnitude and distribution when individuals performed SOS at their preferred speed or were using SBS. We hypothesize that by reducing stair walking speed or by using SBS instead of SOS, patients will reduce the KCF and redistribute the knee loading to avoid the overloading on the involved compartment.

5.2 Methods

Participants

Five participants were recruited for this study via a volunteer database diagnosed in clinical practice with symptomatic bilateral medial knee OA. Eight participants were recruited on a volunteer basis from the university context, who were asymptomatic and had no history of OA (Table 5.1). Participants underwent magnetic resonance imaging (MRI) and complete the Hip (HOOS, Nilsdotter *et al.*, 2003) and Knee (KOOS, Roos and Lohmander, 2003) disability and Osteoarthritis Outcome Score questionnaires. The Research Ethics committee for Science & Engineering at the Metropolitan Manchester University approved the study. Participants signed the written informed consent form prior to participation.

Patients were classified as having mild (1) moderate (2) and severe (3) knee OA based on pain complaints and three parameters observed on the MRI: cartilage defect; bone marrow lesion (BML); and presence of osteophytes. Cartilage was scored for partial and full thickness loss as a % of the surface area in which: 0 when none; 1 when < 15% of cartilage loss; 2 when 15-75% of cartilage loss; 3 when >75% of cartilage loss in a region (medial, lateral or patellofemoral). BML size was scored as follows: 0 when none; 1 when BML size <1 cm; 2 BML when size >1 cm; 3 when multiple BML. Presence of osteophytes was scored based on their size as follow: 0 when no osteophytes; 1 when size < 5mm; 2 when size < 1cm; 3 when > 1cm. All patients presented with bilateral medial knee OA classified as moderate to severe by a consultant radiologist.

Motion Analysis

Motion analysis was performed while barefoot ascending and descending a staircase consisting of seven 17.2cm-height steps (Figure 5.1). A 10-camera 3D motion capture system (Vicon Motion Systems Inc, Los Angeles, CA, USA) synchronized with four force platforms (embedded in the middle of the staircase) recorded the 3D position of 34 reflective markers according to an extended lower-body plug-in-gait marker set protocol (Davis *et al.*,

1991) at 100 Hz, and measured ground reaction forces (GRF) at 1000 Hz (Kistler, Amherst, New York, United States). GRF were filtered using a second order Butterworth low pass filter, with cut-off level at 30Hz, and marker trajectories using a smoothing spline with cut-off at 6Hz.

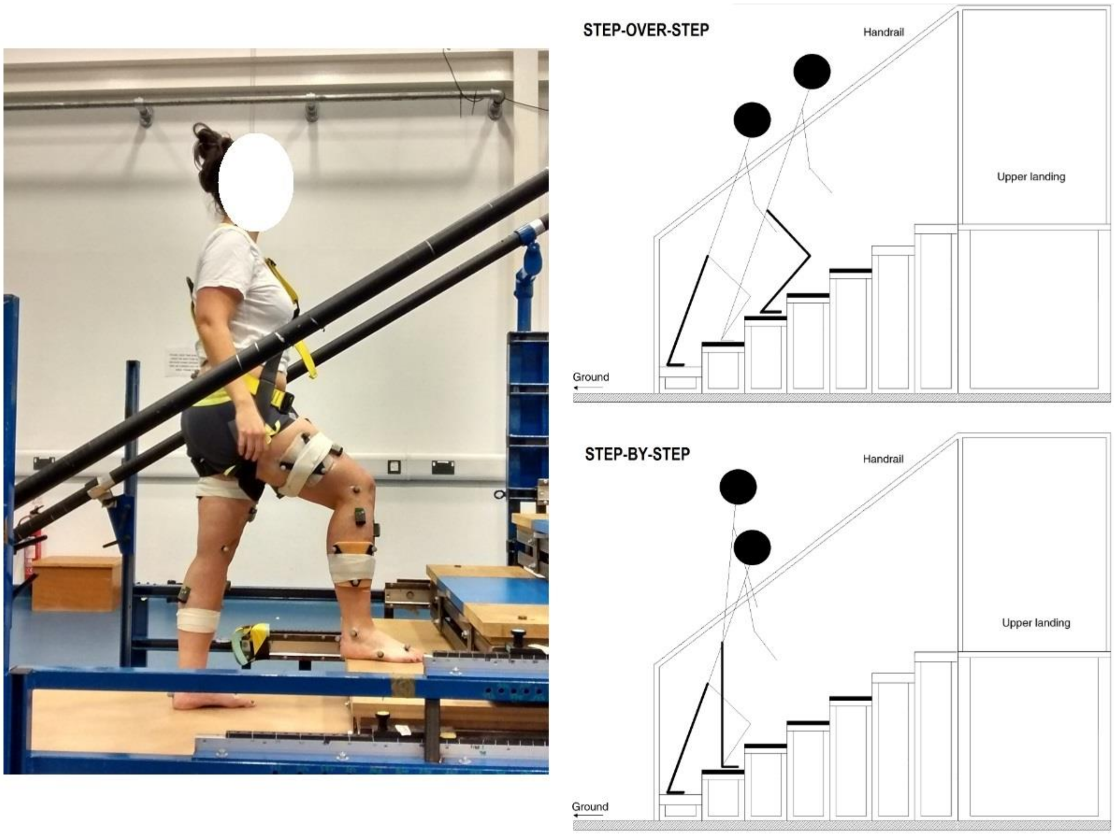

Figure 5. 1 - Marker set on a representative subject while ascending the staircase (left) and a representative scheme of the step-over step (above right) and step-by-step (below right) tasks.

Six trials per condition were collected for ascending and descending for SOS at controlled speed, i.e. alternating feet per step (Figure 5.1, left) with cadence controlled by a metronome at 90 beats per minute, corresponding to the normal self-selected stair walking speed in healthy subjects (Spanjaard *et al.*, 2007). Furthermore, two alternative strategies were tested: SOS at self-selected speed; and SBS, i.e. both feet per step (Figure

5.1, right). The use of the handrail was not allowed. For safety reasons, patients wore a harness during the data collection.

Musculoskeletal Model

A multi-body knee model with 6 degrees of freedom for the tibiofemoral and patellofemoral joints and fourteen ligaments was used (Lenhart *et al.*, 2015). The model includes also an elastic foundation formulation (Bei and Fregly, 2004) to compute cartilage contact pressures. This model was integrated into an existing lower extremity musculoskeletal model (Arnold *et al.,* 2010) with 44 musculotendon units.

The lower extremity model was scaled to subject-specific segment lengths as determined in a static calibration trial. The joint angles were computed using an inverse kinematics algorithm. The concurrent optimization of muscle activations and kinematics (COMAK) algorithm (Lenhart *et al.*, 2015; Smith *et al.*, 2016), was used to compute the secondary tibiofemoral and patellofemoral kinematics, muscle and ligament forces, and contact forces by minimizing the muscle volume weighted sum of squared muscle activations plus the net knee contact energy. Subsequently, an inverse dynamics algorithm computed the external joint moments.

Calculated KCFs were normalized to body weight (BW) and moments to the product of body weight and height (BW×Ht). All data were time normalized to the stance phase (*i.e.* from initial contact to toe off collected from either of the four force plates).

Data analysis

KCF, moments and angles throughout the stance phase were averaged over all trials for each leg. Trunk angles were calculated relative to the ground reference frame. The highest peaks during the first and second half of the stance phase for stair ascent and descent respectively, were determined for the total (TKCF), medial (MKCF), and lateral KCF (LKCF). The highest peak KFM, KAM were determined for all activities whereas peak knee rotation moment (KRM) were only clear for SOS tasks while ascending. Furthermore, maximum contact pressures and the locations of the centers of contact pressure (CoP) in the medial compartment were assessed at the instant of peak MKCF.

Statistical analysis

Independent-samples *t*-test (SPSS Inc., v17.0) evaluated the significance ($P < 0.05$) of the differences in peaks and CoP locations (variables tested for normality by Kolmogorov-Smirnov and Shapiro-Wilk) between the two groups and paired-samples *t*-test between strategies (SOS at controlled *versus* self-selected speed, and SOS *versus* SBS) within each group.

As maximum contact pressures did not show a normal distribution, the non-parametric Mann-Whitney-U test was used to evaluate the significance ($P < 0.05$) of the differences between the two groups and Wilcoxon matched-pair test ($P < 0.05$) between strategies (SOS at controlled *versus* self-selected speed, and SOS *versus* SBS) within each group.

5.3 Results

Descriptive parameters

Age, body mass and height, and also speed did not differ significantly between the two groups (Table 5.1). The medial OA group had significantly more knee pain ($P < 0.001$) than controls.

Table 5. 1 - Characteristics of the groups: control and medial OA.

	Mean (SD)				***P***
	Control		**Medial OA**		**(Control *vs* OA)**
No. of subjects	8		5		-
No. of limbs	16		10		-
Age, *years*	51.0 (13.4)		52.8 (11.0)		0.806
Body mass, *kg*	74.1 (13.7)		83.8 (14.8)		0.255
Height, *m*	1.66 (0.10)		1.70 (0.11)		0.489
KOOS score, %	96.7 (6.0)		42.3 (7.7)		**0.000**
KOOS pain score, %	96.5 (7.8)		41.1 (13.4)		**0.000**
HOOS score, %	98.2 (4.6)		92.8 (10.4)		0.214
	Lat	**Med**	**Lat**	**Med**	
Cartilage score	0	0	0.6	1.8	
BML	0	0	0.3	2	
Osteophytes	0	0	1.2	1.6	
K&L score	0		2-3 (4 out of 5)		

Cont.			Mean (SD) Control	Mean (SD) Medial OA	*P* (Control *vs* OA)		*P* (Control)	*P* (OA)
Speed, *m/s*	**Ascending**	**SOS CS**	0.59 (0.02)	0.57 (0.04)	0.107	***P* (CS *vs* SS)**	**0.006**	**0.031**
		SOS SS	0.53 (0.08)	0.49 (0.12)	0.364			
		SBS	0.36 (0.04)	0.38 (0.03)	0.203	***P* (SOS *vs* SBS)**	**0.000**	**0.009**
	Descending	**SOS CS**	0.60 (0.03)	0.56 (0.08)	0.154	***P* (CS *vs* SS)**	0.180	0.107
		SOS SS	0.57 (0.09)	0.49 (0.11)	0.057			
		SBS	0.34 (0.05)	0.36 (0.04)	0.303	***P* (SOS vs SBS)**	**0.000**	**0.008**

Lat and Med correspond to the lateral and medial compartment of the knee joint, respectively.

SOS CS and SOS SS correspond, respectively, to the step-over-step at controlled speed and at self-selected speed, and SBS to step-by-step.

Statistically significant differences ($P < 0.05$) between the two groups of subjects, evaluated by the independent *t*-test, are indicated in bold.

Statistically significant differences ($P < 0.05$) between strategies (CS *vs* SS, and SOS *vs* SBS) within each group of subjects, evaluated by the paired-sample *t*-test, are indicated in bold.

Comparison between control subjects and medial OA

During SOS at controlled speed, individuals with OA exhibited lower peaks in MKCF ($P < 0.000$) and LKCF ($P = 0.015$) compared to controls during stair ascent (Figure 5.2). During stair descent, on the other hand, no significant differences in the peak MKCF and LKCF (Figure 5.2) were observed between the two groups (Figure C.1 and Table C.1 – Part C.1 – Appendix C).

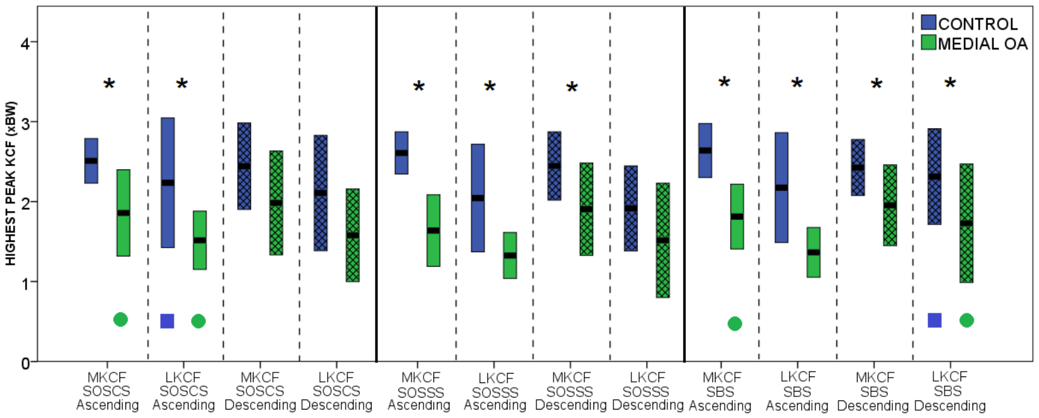

Figure 5.2 - Peak MKCF and LKCF, comparing the two groups of subjects while performing different tasks: SOS at controlled speed (SOS CS), SOS at self-speed (SOS SS) and SBS while ascending or descending stairs. * indicates a significant difference between the groups. ■ indicates a significant difference between the task in which there is this indication and the task SOS while ascending stairs for the control group, whereas ● is used to the OA group.

During SOS at controlled speed, the maximum contact pressures were dropped in individuals with OA, during stair ascent, however, not statistically significant (Table 5.2). In addition, in individuals with OA, the CoP was localized more medially (P = 0.019) in the knee medial compartment compared to controls (Table C.3 – Part C.2 – Appendix C). Controls showed a large decrease in pressure (Figure 5.4) between ascending and descending, whereas for OA there was an increase in pressure from ascending to descending.

During SOS at controlled speed, individuals with OA exhibited significantly lower peak KFM compared to controls during stair ascent (P = 0.002) and descent (P = 0.022) (Table C.5 and Figure C.5 – Part C.3 – Appendix C). No significant differences in the peak KAM or KRM were observed between the two groups.

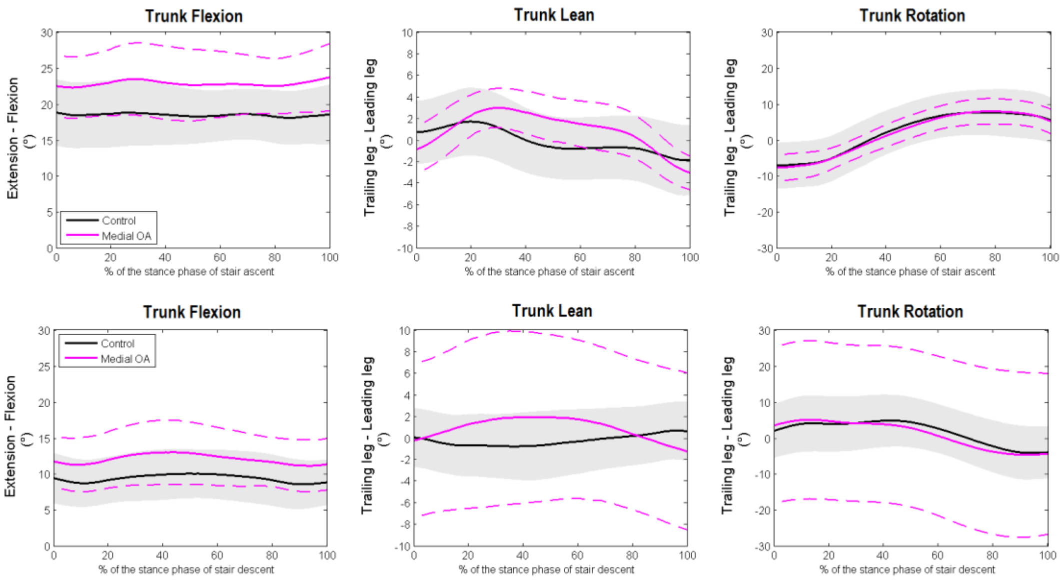

Figure 5. 3 - Trunk kinematics relative to the ground reference frame in the sagittal (left), frontal (middle) and transversal (right) plane for SOS while ascending (above) and descending (below) stairs at controlled speed during stance phase, comparing healthy subjects and individuals with medial knee OA.

During SOS at controlled speed, individuals with OA had higher trunk flexion angles and tended to lean the trunk more towards the leading leg in the frontal plane throughout the stance phase compared to controls during both stair ascent and descent (Figure 5.3). During stair descent, the OA group exhibited a larger variation in the trunk kinematics in the frontal and transversal planes compared to controls. The higher trunk flexion angles observed in patients with OA were statistically significant during stair ascent (P = 0.001). Similarly, although not statistically significant, the difference in trunk bending angles between the groups was higher during stair ascent than descent (Table C.6 - Part C.4 - Appendix C). In all planes of motion, kinematics of the hip, knee and ankle joints showed a similar pattern of movement between the two groups during stair ascent and descent (Figure C.8 and C.9 – Part C.4 – Appendix C).

Table 5. 2 - Maximum contact pressures (MPa) at the peak MKCF comparing the two groups of subjects and p- values comparing activities into the groups.

		Mean (SD)		***P*** **(C0 vs OA)**
		Control (16 legs)	**Medial OA (10 legs)**	
SOS CS	**Ascending**	24.1 (12.1)	16.0 (6.1)	*0.092*
	Descending	15.8 (5.6)	14.2 (4.6)	*0.598*
SOS SS	**Ascending**	24.4 (11.7)	13.9 (4.6)	***<u>0.004</u>***
	Descending	15.7 (7.1)	13.8 (4.6)	*0.317*
SBS	**Ascending**	24.4 (12.6)	14.7 (4.6)	***<u>0.035</u>***
	Descending	16.1 (5.9)	11.4 (3.3)	***<u>0.013</u>***
Ascending	***P*** **(SOS SS *vs* SOS CS)**	*0.717*	*0.093*	
	P **(SOS SS *vs* SBS)**	*0.877*	*0.059*	
Descending	***P*** **(SOS SS *vs* SOS CS)**	*0.959*	*0.445*	
	P **(SOS SS *vs* SBS)**	*0.877*	***<u>0.007</u>***	

Statistically significant differences (P < 0.05) in maximum contact pressures between the two groups of subjects, evaluated by Mann-Whitney-U test, are indicated in bold.

Statistically significant differences (P < 0.05) in maximum contact pressures between strategies within each group of subjects, evaluated by Wilcoxon matched-pair test, are indicated in bold.

SOS CS, SOS SS and SBS correspond to step-over-step at controlled and self-selected speed, and step-by-step, respectively.

Comparison between strategies: SOS at controlled versus self-selected speed

In both groups, the self-selected speed was lower than in the controlled condition, however only significantly during stair ascent.

With decreased speed, the peak LKCF decreased (P = 0.009) during stair ascent in healthy subjects (Figure C.3 and Table C.2 – Part C.1 – Appendix C), whereas in individuals with OA (Figure C.4 and Table C.2 – Part C.1 – Appendix C), the peak MKCF (P = 0.024) and LKCF decreased (P = 0.002). No significant differences in KCF were observed between controlled and self-selected execution for stair descent in healthy or OA groups.

As the speed decreased, KCF were decreased in OA patients during stair ascent and significant lower peak MKCF (P < 0.001) and LKCF (P = 0.015) compared to controls were maintained. However, during stair descent at self-selected speed, peak MKCF (P = 0.011) was significantly reduced in OA group compared to controls (Figure C.2 and Table C.1 – Part C.1 – Appendix C).

As the speed decreased, OA patients demonstrated significantly lower maximum contact pressures (Table 5.2) during stair ascent (P = 0.004).

As the speed decreased, CoP significantly shifted to a more medial region in the medial tibial plateau (Figure 5.4) in controls (during both stair ascent (P < 0.001) and descent (P = 0.033)). On the other hand, in individuals with OA, the CoP shifted to a more lateral region (P = 0.034) during stair ascent (Table 4 – *Part 2 – SM*) and remained in a similar location during stair descent.

Differences in the external moments between the two groups were comparable in the self-selected condition to those observed at controlled speed (P = 0.002 for KFM) (Table C.5, and Figure C.6 and C.5 – Part C.3 – Appendix C).

The increased trunk flexion and lean angles towards the leading leg were maintained in both controlled and self-selected speed (Figure C.7 – Part C.4 – Appendix C) during stair ascent. As the speed decreased, the difference in trunk bending angles between the groups was even higher than at controlled speed, resulting in statistically significant differences during stair ascent (P = 0.048). During stair descent, on the other hand, OA patients exhibited a smaller variation in the trunk kinematics in the frontal and transversal planes as the speed decreased. As the speed decreased, the difference in trunk flexion angles between the groups was even higher than at controlled speed during stair descent, being statistically significant (P = 0.001). Both groups presented similar hip, knee and ankle kinematics during both tasks while ascending (Figure C.8 and C.10 – Part C.4 – Appendix C) and descending (Figure C.9 and C.11 – Part C.4 – Appendix C).

Comparison between strategies: SOS versus SBS

When performing SBS instead SOS, both controls and OA significantly reduced the speed while ascending ($P < 0.001$ and $P = 0.009$, respectively) and descending stairs ($P < 0.001$ and $P = 0.008$, respectively) (Table 5.1). Both controls ($P = 0.016$) and OA ($P = 0.040$) exhibited significantly higher peak LKCF when using SBS instead of SOS during stair descent. During stair ascent, however, individuals with knee OA significantly increased the peak MKCF ($P = 0.008$) when using SBS, whereas no significant differences were seen in controls (Table C.2 – Part C.1 – Appendix C). During stair ascent using SBS ($P < 0.001$ and $P = 0.004$, respectively, medial and lateral) and SOS ($P < 0.001$ and $P = 0.002$, respectively, medial and lateral), the OA group had significantly lower KCF compared to controls in both compartments. During stair descent using SBS, on the other hand, OA patients exhibited higher reduction ($P = 0.009$) in MKCF than during SOS ($P = 0.011$) and also reduced LKCF ($P = 0.037$) (Table C.1 – Part C.1 – Appendix C).

By altering from SOS to SBS, maximum CP were not significantly different neither in controls or patients with OA (Figure 5.4 and Table 5.2) during stair ascent. However, during stair descent maximum CP significantly decreased in patients with OA when using SBS ($P = 0.007$). When comparing controls to OA patients while performing SBS (Table 5.2), a lower maximum CP were found in patients during stair ascent ($P = 0.035$) (as observed during SOS, $P = 0.004$) and also during stair descent ($P = 0.013$) (differently from SOS, $P = 0.319$).

In controls, CoP shifted to a more lateral region on the medial tibial plateau (Figure 5.4) when changing from SOS to SBS, being significant during stair descent (P < 0.001). In OA patients, the CoP shifted to a more medial (P = 0.011) and posterior (P = 0.005) region on the medial tibial plateau (Figure 5.4) during stair ascent and a more posterior (P = 0.019) region during stair descent when changing from SOS to SBS (Table C.4 – Part C.2 – Appendix C).

Use of SBS resulted in similar differences in the external moments between the groups observed during SOS: OA patients maintained significantly reduced peak KFM compared to controls during both stair ascent (P < 0.001) and descent (P = 0.001). Similarly, no significant differences between the groups were found in KAM during SBS (Table C.5 – Part C.3 - Appendix C).

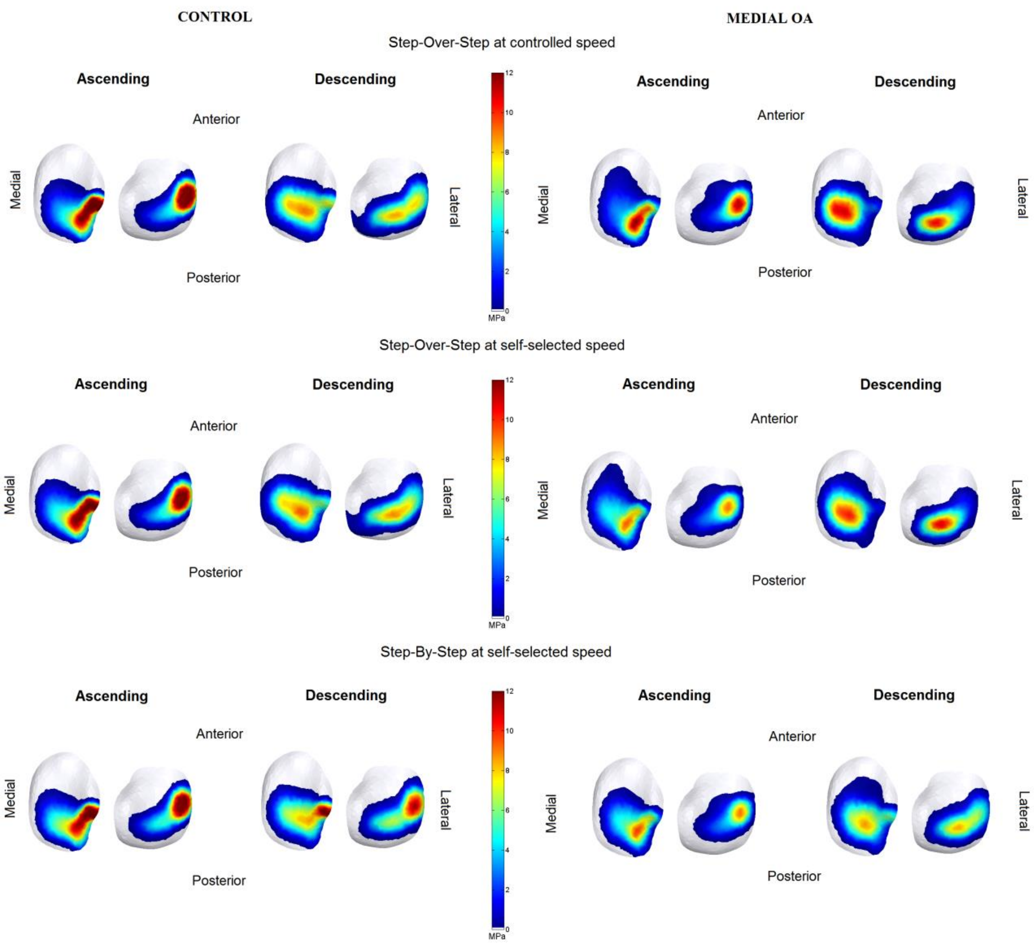

Figure 5.4 - Averaged contact pressure distributions on the articular surfaces of medial and lateral of the tibia plateau at the time instant of the first peak

MKCF during SOS at controlled speed; SOS at self-selected speed and SBS, while ascending and descending stairs. Results are presented for the healthy group (on the left), and the medial knee OA group (on the right).

5.4 Discussion

This study investigated the magnitude of KCF and cartilage pressures during stair ascent and descent in individuals with medial knee OA. Using a multibody musculoskeletal model, we showed that patients with OA exhibited reduced tibiofemoral loading during stair ascent, but not stair descent. The reduced contact force during ascent was achieved by increasing the trunk flexion angle, which reduced the knee flexion moment and thus muscle forces compressing the joint. This strategy was not as effective in stair descent, where the trunk is more vertical, thus the knee flexion moment cannot be modulated without large adjustments to trunk flexion that compromise stability. Furthermore, different strategies in stair negotiation, such as reduction in speed, and employing SBS instead of SOS were shown to be effective in reducing the knee contact loading.

Our results confirmed the hypothesis that OA patients would present lower KCF than controls. During stair ascent**,** when asked to walk at certain speed, which was significantly higher than their preferred speed, the OA group exhibited reduced both peak MKCF and LKCF. The OA group exhibited higher trunk flexion and higher trunk lean towards the leading leg compared to controls. By positioning the centre of mass further forwards and more towards the leading leg at a time where the knee joint is considerably flexed and potential for high joint moment, OA patients direct the GRF vector closer to the knee joint centre and, therefore, reduce the KFM (significantly) and KAM. In addition, the increased trunk flexion decreases the demand of the knee extensors, which generate the propulsion required during stair ascent. Previous studies have also found reduced KFM (Kaufman *et al.*, 2001; Asay *et al.*, 2009) and increased trunk flexion (Asay *et al.*, 2009) during stair ascent (Kaufman *et al.*, 2001; Asay *et al.*, 2009) and descent (Kaufman *et al.*, 2001) in OA patients. Reduction in the peak KFM observed in OA patients during demanding functional activities as stair ascent and descent has been attributed to the loss of quadriceps function and strength, a common clinical finding in elderly (Tzankoff and Norris, 1978; Lindle *et al.*, 2007) and associated to knee OA (Ling *et al.*, 2007; Rudolph *et al.*, 2007).

Despite the reduced KCF, OA patients still reported significantly higher pain complaints compared to controls. Our study is therefore the first one to determine how the altered stair walking pattern used by patients with OA, such as higher trunk flexion and reduced KFM, is reflected in the compartmental KCF.

During stair descent**,** the compensatory mechanisms used by the OA group were less effective in reducing the knee loading than during stair ascent, since reductions in peak MKCF and LKCF (compared to controls) were not statistically significant. Patients could not increase the trunk flexion or the trunk lean towards to the leading leg during stair descent as much as they did during stair ascent compared to a healthy control, probably due to fear of falling. During stair descent, the body has to adopt to a more upright position to maintain balance and, therefore, by leaning the trunk too far forwards, patients could compromise their balance (Schindler and Scott, 2011) and, ultimately fall. The inability to reduce KCF during descent may explain why patients experience higher levels of knee pain (Brandt *et al.*, 2003) during stair descent than ascent.

The second hypothesis that OA patients would be able to reduce the KCF by reducing the speed or by using SBS instead of SOS has been partially confirmed. When subjects walked at their preferred speed, which was significantly slower during stair ascent, differences in KCF between OA patients and controls were higher during both stair ascent and descent. Furthermore, during stair descent, a significant reduction in the peak MKCF were observed in the OA group compared to controls at self-selected speed, which was not present at controlled speed. Likewise, during stair descent, only when forced to increase their speed, some OA patients felt forced to rotate their trunk more in the frontal and transversal planes resulting in a high variation in the trunk kinematics in these two planes. This shows that some patients felt forced to use another mechanism rather than increased trunk flexion to perform stair descent when speed was enforced. This suggests that it is more effective for patients to reduce medial compartment loading during stair descent by reducing the walking speed than to alter trunk kinematics. During stair ascent, on the other hand, the changes in the trunk kinematics were still effective for OA patients to reduce knee loading, even at a higher stair walking speed. In addition, speed reduction allowed OA patients to decrease maximum medial compartment contact pressure and to shift the medial CoP location more laterally. Thus, a reduction in speed together with changes in trunk kinematics are the key strategies used to reduce the knee loading during stair ascent, and a reduction in speed is even more important to efficiently reduce the MKCF during stair descent.

Surprisingly, by performing SBS instead of SOS during stair ascent, OA patients significantly increased the MKCF, even when the speed was significantly lower. However, during stair descent, by performing SBS instead of SOS, they significantly decreased the medial knee contact pressures. Similarly, Reid *et al.* (2009) reported that in healthy subjects, SBS strategy was more efficient in reducing the peak KFM when compared to SOS strategy during stair descent than stair ascent. Our study suggests that individuals with OA, in contrast to healthy subjects, shifted the medial CoP to a more medial region during stair ascent when performing SBS. During stair descent, however, no difference was found in OA patients between SBS and SOS in the medial-lateral direction, whereas controls shifted the medial CoP more laterally. This is indicative that adaptations in stair walking strategy seen in OA patients have more impact on the loading distribution during stair ascent than descent. From our findings, it is suggested that, in OA patients, SBS is only effective in reducing the medial knee loading during stair descent, but not during stair ascent.

The magnitude of KCF in healthy subjects seen in the present study was higher for stair ascent than those from literature based on measured KCF in subjects with instrumented prosthesis (Kutzner *et al.*, 2010; Heinlein *et al.*, 2008). Our controls exhibited an averaged peak TKCF of 4.41 (0.78) BW and 4.20 (0.74) BW for, respectively, stair ascent and descent, whereas Kutzner *et al.* (2010) reported averages of 3.16 BW and 3.46 BW for the peak resultant force. Similar results, ranged from 2.90 to 3.50 BW, were reported by Heinlein *et al.* (2008). More similarly, our OA group exhibited peak KCF of 2.78 (0.62) BW and 3.29 (1.14) BW for, respectively, stair ascent and descent. Previous simulation studies on healthy subjects and those having TKR during stair ascent, presented compressive joint reaction forces up to 4.00 BW (Rasnick *et al.*, 2016). Differences might be due to several reasons: instrumented implant studies report on patients having TKR and an altered gait pattern may therefore be present; none of the mentioned studies report stair walking speed nor the step height. It is important to mention also that our model does not account for OA induced changes in the articular geometry, thickness and mechanical properties of the cartilage or changes in the ligaments. In addition, co-contraction patterns that have been reported in individuals with knee OA and may heighten loading (Hubley-Kozey *et al.*, 2009) were not taken in account in our approach and consequently KCF calculated for these patients might be underestimated.

5.5 Conclusions

During stair ascent, OA patients could effectively reduce the knee joint loading by increasing the trunk flexion and lean the trunk more towards the leading leg. However, during stair descent, changes in the trunk flexion and frontal lean were less effective, requiring reduced speed or even more increased trunk rotation and lean to effectively reduce the peak MKCF and the contact pressures on the tibia plateau. Furthermore, this study suggests that, in OA patients, SOS is more effective in reducing the medial knee loading, particularly at reduced speed, during stair ascent, while SBS is more effective during stair descent.

Author contributions

All authors take responsibility for the integrity of the work as a whole, including data and accuracy of the analysis. Design: S. Meireles, N. Reeves and I. Jonkers. Conception: S. Meireles, N. Reeves, R. Jones, C.R. Smith, D.G. Thelen and R. Hodgson. All the authors contributed to the **a**nalysis and interpretation of the data, drafting of the article and final approval of the article.

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Competing interests

All authors declare no conflict of interest.

5.6 References

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Chapter 6

Discussion and conclusions

6.1 Overview

In the specific discussion, the main findings for each research question are summarized addressing the respective hypotheses formulated in the introduction. Thereafter, the general conclusions are stated and the limitations of the studies are discussed. Finally, some suggestions for future research are formulated.

The overall objective of this PhD was to evaluate the knee joint loading accounting not only for the external forces but also muscle and ligament forces, using musculoskeletal modelling workflows during common daily-living activities such as walking and more demanding tasks, such as curb step-up and stair negotiation in individuals with varying severities of medial knee OA.

6.2 Specific Discussion

Knee contact forces are not altered in early knee osteoarthritis

In study I, knee loading was assessed by calculating knee contact forces and their associations with knee external adduction and flexion moments during the stance phase of walking in patients with early knee osteoarthritis. We aimed to investigate whether altered knee loading was already present in early stages of this disease. These patients were classified based on early joint degeneration visualized only by MRI. Knee loading estimated for patients with early medial knee OA was then compared to healthy subjects as well as patients with established medial knee OA.

Hypothesis I

In the presence of early signs of structural degeneration as present in early OA subjects, knee loading is increased compared to healthy subjects but to a lesser extent than in established OA subjects.

The hypothesis I was partially rejected by the results since mechanical loading was not significantly increased in individuals with early knee OA compared to controls, as expected, but only in established knee OA compared to controls and early OA. No differences were observed in the external moments (KAM or KFM) or in the total KCF between individuals with early knee OA and healthy subjects. These findings are in line with Baert *et al.* (2013) and Duffell *et al*. (2014), who did not find differences in KAM between early OA and healthy subjects. We could, therefore, further conclude that not only KAM was not increased in subjects that only present early signs of structural joint degeneration but also no signs of increased overall knee loading are present. The contribution of the overall biomechanical overloading to early stages of knee OA cannot be confirmed. Consequently, the potential use of the total knee contact forces during walking to detect early OA cannot confirmed. Patients with established knee OA, on the other hand, exhibited higher mechanical loading compared to early OA subjects as well as to healthy subjects. Indications for higher knee loading were statistically confirmed in terms of increased knee contact force impulses, which are representative for the cumulative effect of increased loading magnitude and prolonged stance duration in the established OA group. Similar to previous studies (Baert *et al.*, 2013; Kumar *et al.*, 2013; Richards *et al.*, 2010), the tendency of increased KAM (resulting into a p = 0.038 when the 3 groups were compared), KFM and KCF (being significantly increased during single stance) was also observed in established OA. Therefore, as hypothesized, overloading is more prevalent in established knee OA than at early stages, and further support the presence of increased loading in later stages of OA, where more structural joint degeneration is present.

Hypothesis II

Alterations in knee loading associated with different levels of joint degeneration generate differences in the contribution of altered frontal and sagittal plane moments. In early OA patients, presenting limited structural degeneration, frontal plane moments contribute less to the observed changes in knee loading compared to patients with established OA.

Confirming part of the hypothesis II, peak KCFs are differently influenced by the frontal and sagittal knee moments depending on the level of structural joint degeneration. When initial structural degeneration is present, KFM contributes more to the KCF. When structural degeneration increases, the contribution of KAM also increases during the first part of the stance phase. However, the hypothesized higher contribution of KAM to the knee loading of patients with established OA compared to the early OA could not be confirmed. Indeed, during the first part of the stance phase and into midstance, KAM contributed even more to the observed changes in the KCF in patients with early and established knee OA than in controls. However, during the second part of the stance phase, KAM was a poor contributor to the peak KCF in both group of patients. Although the first peak KCF is predicted well by KAM irrespective the presence of OA, multiple regression results show that a combination of KAM and KFM better predicts KCF than KAM or KFM alone, which is in agreement with previous studies (Kumar *et al.*, 2013; Walter *et al.*, 2010). We can, therefore, conclude that both frontal and sagittal plane moments need to be considered to estimate KCF. However, in established OA patients, the variance accounted for when combining KAM and KFM is still low (20%) during second part of the stance phase. This highlights the important role of muscle action controlling flexion-extension moments in joint loading during late stance.

Differences in knee adduction moment between healthy subjects and patients with osteoarthritis depend on the knee axis definition

In study II, the effect of using a transepicondylar *versus* a functional axis of rotation on knee adduction moment was evaluated in patients with varying severities of medial knee OA. The effect of using weight-bearing *versus* non-weight-bearing condition on KAM in patients with medial knee OA was also assessed. Finally, the impact of selecting one of these methods on the differences in KAM between controls and patients was evaluated.

Hypothesis III

The use of the transepicondylar axis *versus* functional axis of rotation influence the differences in KAM between groups presenting varying severity of knee OA and healthy subjects.

Our findings confirmed the hypothesis III. The cross-talk effect observed when the transepicondylar axis was used, as reflected by the unrealistic high abduction angles at peak knee flexion during gait, caused a significant increased first peak KAM in individuals with established knee OA compared to controls. The use of a functional axis of rotation, on the other hand, effectively corrected this cross-talk effect, confirming the results of previous studies (Schwartz *et al.,* 2004), eliminating that significant increased peak KAM found in the established OA group. By using a FAR, frontal plane range of motion was reduced even presenting a reversal of the abduction motion, in both stance and swing phase. Excessive abduction angles during gait, especially those coinciding with peak knee flexion during the swing phase, have been indicated to result from cross-talk (Baudet *et al.*, 2014; Passmore and Sangeux, 2016). Therefore, our results imply that the use of FAR effectively reduces cross-talk. In addition, FAR models result in knee adduction during most of the gait cycle reaching the maximum knee adduction angles during the swing phase in agreement with previous literature (Kadaba *et al.*, 1990, Desloovere *et al.*, 2010, Scheys *et al.*, 2013). The reduced cross-talk effect when using FAR confirmed the hypothesis III, since first peak KAM was reduced when using FAR compared to TEA, up to a point where significant differences between the different groups were no longer present. This was especially pronounced in established OA, where the first and second peak KAMs calculated using FAR obtained from a non-weight-bearing motion were significantly lower compared to the TEA models.

Hypothesis IV

Knee adduction moment calculated using FAR during weight-bearing motion is significantly different from those calculated using FAR during non-weight-bearing motion. The presence of structural changes and unstable knee joints observed in patients with established OA might have a higher effect during weight-bearing conditions.

Our results confirmed the hypothesis IV. The differences found in the KAM by using different FAR were especially pronounced in the established OA group, where the first and second peak KAMs calculated using nwFAR were significantly lower compared to the TEA models and to the wFAR models. The differences in the KAM, due to the differences in FAR calculated in weight-bearing and non-weight-bearing is relevant as tibiofemoral kinematics is known to be load-dependent (Markolf *et al.*, 1981; Dyrby and Andriacchi, 2004), and therefore the position and orientation of a functionally identified AoR are likely to differ between activities with variable loading conditions. Subjects with established OA**,** presented FAR that were more adduction oriented (with respect to the femur reference frame) during weight-bearing compared to non-weight-bearing conditions as reflected in the significant differences in the orientation around the ab-adduction axis between wFAR and nwFAR models. Confirming our hypothesis and suggesting that in patients presenting structural degeneration, the FAR orientation calculated in weight-bearing is indicative of a more adducted joint alignment. Therefore, the higher adduction orientation found in wFAR models better reflects load-dependent knee kinematics, which has been shown to be especially important for patients with end-stage knee OA (Dyrby and Andriacchi, 2004).

Medial knee loading is increased in subjects with early OA compared to healthy controls during gait but not during step-up-and-over task.

In study III, knee loading was assessed by calculating the compartmental knee contact forces (in the medial and lateral knee compartment) and medial contact pressures, during the stance phase of walking as well as step-up-and-over activities. Patients having early medial knee osteoarthritis, revealed only on MRI (Luyten *et al.*, 2012), were evaluated and compared to those having established medial knee OA and asymptomatic subjects.

Hypothesis V

Medial KCF and contact pressure distributions rather than knee joint moments are more sensitive in detecting early changes in knee joint loading in subjects with early medial knee OA, prior to the onset of structural degeneration.

The hypothesis IV was partially confirmed. Whereas overall total KCF was increased, only the first peak medial KCF was significantly increased in patients with early OA compared to control subjects. Only patients with established OA presented significantly increased peaks in the total KCF together with a significant first peak medial KCF. Likewise, although the maximum CP during the peak medial KCF have increased in both groups of patients compared to controls, it was only significant in established OA. Nevertheless, both groups of patients showed a shifted CoP at the first peak medial KCF which, in combination with increased external rotation of the tibia during early stance, shows that patients with knee OA tend to load a more posterior (both groups) and lateral (established OA) cartilage region of the medial tibia plateau, which is not loaded in healthy subjects. This suggests that, although excessive loading is not revealed by the total KCF in the early stages of OA, as already observed in our study I, the medial-lateral forces distribution and pressure distribution are altered. Only when clear structural degeneration is present, as in the established OA group, changes in gait kinematics that result in excessive total knee loading occur. The abnormal transverse plane kinematics, particularly the increased of the external rotation in patients, shifted the normal load bearing contact to regions in the cartilage that are less predisposed to higher loads and therefore might influence the initiation of OA. Similar to previous studies (Gok *et al.*, 2002; Wilson *et al.*, 2013), who found higher KRM in patients with knee OA compared to controls, the first peak KRM was increased in patients with knee OA compared to healthy subjects. For patients with established OA, the excessive KRM persisted during late stance.

Hypothesis VI

Higher demanding activities may already cause larger alteration in the medial compartment loading, present prior to alterations during gait and, therefore, may allow discriminating patients with early knee OA from healthy subjects.

In contrast to the hypothesis VI, no significant differences were observed in knee loading between patients with early knee OA and healthy subjects during step-up-and-over. High variations in movement strategies between subjects, particularly in those having knee OA, were observed during step-up-and-over, preventing to find statistical differences in kinematics and loading patterns between groups. This high variation might be due to the difficulty of standardizing the movement performance. Being a more demanding but not repetitive task, step-up-and-over seems to motivate subjects, particularly those with knee OA, to search more alternative movement strategies to deal with and, therefore, introducing more movement variability. Nevertheless, although differences were not statistically significant between the groups, it was clear that patients with established OA exhibited a different loading pattern particularly in the medial compartment. Their highest peak medial KCF was delayed and most patients only presented a single peak during the stance phase. This difference in the loading pattern observed in patients with established OA needs further analysis. Finally, in line with previous studies in stair negotiation (Hurley, 1998; Slemenda *et al.*, 1997; Kaufman *et al.*, 2001; O'Reilly *et al.*, 1998), individuals with established knee OA also showed reduced first peak KFM compared to the control and the early knee OA group during the upward propulsive phase (step ascent). This is an indication that these individuals seem to present a compensatory mechanism during step-up that was not used during gait.

Patients with medial knee osteoarthritis reduce medial knee contact forces by altering trunk kinematics, progression speed, and stepping strategy during stair ascent and descent

In study IV, joint kinematics and knee loading, assessed by calculating compartmental KCF and medial contact pressures, were evaluated in patients with medial knee OA during stair ascent and descent while performing the traditional step-over-step motion pattern at controlled speed. Controls and individuals with knee OA performed the tasks with cadence close to the reported self-selected stair speed in healthy subjects (Spanjaard *et al*., 2007), which is expected to be higher than the self-selected speed used by patients. Ultimately, compartmental KCF and contact pressures were also assessed while performing two more different strategies in stair negotiation: SOS at self-selected speed and step-by-step, and compared between the two groups.

Hypothesis VII

Individuals with medial knee OA present lower knee loading than healthy subjects during stair negotiation trying to avoid pain.

Our results confirmed the hypothesis that OA patients would present lower KCF than controls. During stair ascent, when asked to walk at certain speed, which was significantly higher than their preferred speed, individuals with medial knee OA exhibited reduced peak KCF in both medial and lateral compartments. Individuals with knee OA exhibited higher trunk flexion and higher trunk lean towards the leading leg compared to healthy subjects. By positioning the centre of mass further forwards and more towards the leading leg at a time where the knee joint is considerably flexed and potential for high knee joint moment, patients direct the GRF vector closer to the knee joint centre and, therefore, reduce the KFM (significantly) and KAM. In addition, the increased trunk flexion will decrease the demand of the knee extensors, that help with the propulsion required during stair ascent. Previous studies have also found reduced KFM (Kaufman *et al.*, 2001; Asay *et al.*, 2009) and increased trunk flexion (Asay *et al.*, 2009) during stair ascent (Kaufman *et al.*, 2001; Asay *et al.*, 2009) and descent (Kaufman *et al.*, 2001). Reduction in the peak KFM observed in patient with knee OA during demanding functional activities as stair ascent and descent has been attributed to the loss of quadriceps function and strength, a common clinical finding in elderly (Tzankoff and Norris, 1978; Lindle *et al.*, 1997) and associated to knee OA (Ling *et al.*, 2007; Rudolph *et al.*, 2007). Despite the reduced KCF, OA patients still reported significantly higher pain complaints compared to controls. Our study is therefore the first one to determine how the altered stair walking pattern used by patients with OA, such as higher trunk flexion and reduced KFM, is reflected in the compartmental KCF. During stair descent**,** the compensatory mechanisms used by the knee OA group were less effective in reducing the knee loading than during stair ascent, since reductions in the peak MKCF and peak LKCF (compared to controls) were not statistically significant during stair descent. Patients could not increase the trunk flexion or the trunk lean towards to the leading leg during stair descent as much as they did during stair ascent compared to a healthy control, probably due to fear of falling. During stair descent the body has to adopt to a more upright position to maintain balance and, therefore, by leaning the trunk too far forwards, patients could compromise their balance (Schindler and Scott, 2011) and, ultimately, fall. The inability to reduce KCF during descent may explain why patients experience higher levels of knee pain (Brandt *et al.*, 2003) during stair descent than ascent.

Hypothesis VIII

By reducing the stair walking speed or by using SBS instead of SOS, patients will reduce the KCF and redistribute the knee loading to avoid the overloading on the involved compartment.

The hypothesis VIII that patients would be able to reduce the KCF by reducing the speed or by using SBS instead of SOS has been partially confirmed. When subjects walked at their preferred speed, which was significantly slower during stair ascent, differences in KCF between OA patients and controls were higher during both stair ascent and descent. Furthermore, during stair descent, a significant reduction in the peak medial KCF was observed in individuals with knee OA compared to controls at self-selected speed, which was not present at controlled speed. Likewise, during stair descent, only when forced to increase their speed, some patients felt forced to rotate their trunk more in the frontal and transversal planes resulting in a high variation in the trunk kinematics in these two planes. This shows that some patients felt forced to use another mechanism rather than increased trunk flexion to perform stair descent when speed was enforced. This suggests that it is more effective for patients to reduce medial compartment loading during stair descent by reducing the walking speed than to alter trunk kinematics. During stair ascent, on the other hand, the changes in the trunk kinematics were still efficient for patients with OA to reduce knee loading even at higher stair walking speed. In addition, speed reduction allowed OA patients to decrease maximum medial compartment contact pressure and to shift the medial CoP location more laterally. Thus, a reduction in speed together with changes in trunk kinematics are the key strategies used to reduce the knee loading during stair ascent, and a reduction in speed is even more important to efficiently reduce the medial KCF during stair descent. Surprisingly, by performing SBS instead of SOS during stair ascent, individuals with knee OA significantly increased the medial peak KCF, even when the speed was significantly lower. However, during stair descent, by performing SBS instead of SOS, they significantly decreased the knee contact pressures on the medial compartment. Similarly, Reid *et al.* (2007) reported that in healthy subjects, SBS strategy was more efficient in reducing the peak KFM when compared to SOS strategy during stair descent than stair ascent. Our study suggests that individuals with knee OA, in contrast to healthy subjects, shifted the medial CoP to a more medial region during stair ascent when performing SBS. During stair descent, however, no difference was found in patients between

SBS and SOS in the medial-lateral direction, whereas controls shifted the medial CoP more laterally. This is indicative that adaptations in stair walking strategy seen in individuals with OA, have more impact on the loading distribution during stair ascent than descent. From our findings, it is suggested that, in individuals with medial knee OA, SBS is only effective in reducing the medial knee loading during stair descent, but not during stair ascent.

6.3 General Conclusions

The *first main conclusion* of this work is that **knee contact forces provide a more sensitive metric to the overall knee joint loading than joint moments in early and established knee OA**. KCF were significantly increased in individuals with established medial knee OA, although no differences in KAMs were observed between the groups during gait, when taking into account the stance phase duration of loading by calculating impulses (study I). In addition, while the overall KCF was significantly increased in individuals with established medial knee OA and medial KCF was increased in those with early and established medial knee OA, KAM was not significantly different between patients' groups and the control group during the stance phase of gait (study III). In fact, KAM combined with KFM (rather than KAM on its own) was needed to better estimate KCFs (study I). This finding was comparable to what was reported by Kumar *et al.* (2013). Our findings indicate that knee contact forces calculated by a more complex musculoskeletal model provides a more sensitive metric than the KAM used by previous researchers (Fregly *et al.* 2007; Hurwitz *et al.* 2000; Guo *et al.* 2007; Miyazaki *et al.* 2002; Baliunas *et al.* 2002; Lewek *et al.* 2004) to identify individuals presenting medial knee OA. Therefore, better than KAM, KCF might be used as feedback signal during gait retraining sessions aiming at controlling knee loading in patients with knee osteoarthritis (study I). This reinforces the importance of considering the muscle and ligament forces when assessing knee loading rather than only the external knee adduction moment, confirming the main hypothesis of this project.

The *second main conclusion* of this project is that **while comparing different studies assessing KAM in individuals with varying knee OA severities, differences between groups should be interpreted considering the specific knee axis definition** (study II). Our study underlines the sensitivity of KAM to knee axis definition. In many clinical studies, the definition of the knee axis of rotation is considered a methodological detail that is often not reported and in many cases the transepicondylar axis is used to calculate KAM (Newell *et al.* 2008; Ogaya *et al.* 2014; Levinger *et al.* 2013; Thorp *et al.* 2007; Thorp *et al.* 2006; Astephen *et al.* 2008; Landry *et al.* 2007). However, our study indicates that the excessive KAM was (when using TEA) or was not confirmed (when using FAR) in subjects with established OA, depending on the axis of rotation used (study II). Therefore, our findings suggest that differences in axis definition between studies may explain the variability in reported relation between KAM and OA progression and should be considered with care when comparing different study outcomes. This is especially true since excessive KAM observed in subjects with established OA, depends on the knee axis of rotation used to calculate the knee kinematics and ultimately the KAM. Finally, in studies on knee OA, the use of weight-bearing motions should be considered for the calculation of FAR to better account for the load-dependent knee instability.

The *third main conclusion* of this project is that **especially in patients with early stages of OA, the altered knee loading can only be detected by a musculoskeletal model which calculates compartmental loading.** Our study showed that an overall excessive mechanical loading, assessed by the total KCF, is not present during gait in early stages of OA but only in established OA compared to controls (study I and study III). This suggests that overall excessive loading does not contribute to early progression of OA, but only results following structural degeneration. However, when analyzing the knee medial compartment, increased joint loading was already observed during gait in individuals with early medial knee OA, as confirmed by the increased medial KCF, a shift in the center of pressure and increased knee rotation moment (study III). This finding is even more interesting as the early OA group has about 40% of patients with unilateral knee OA, compared to the established OA group in which all patients presented bilateral OA. In patients who experience pain (as those included in the early OA group) and in who only one knee is affected, a decreased knee loading in the affected limb could be expected as a compensatory mechanism of overloading the contralateral limb. Thus, it would be expected to result in lower knee loading since only the affected limbs were included.

Our project extends the findings reported by Kumar *et al.* (2013) in showing the importance of assessing the medial rather than the total KCF, especially in early stages of medial knee OA. As such, our study indicates, firstly, that medial KCF rather than total KCF during gait provides the most sensitive marker to identify early medial knee OA developed prior to the onset of structural changes as show on radiographs. Secondly, only when structural degeneration occurs, as in individuals with established knee OA, an increased overall joint loading, affecting not only the medial but also the lateral compartment of the knee joint, is observed.

The *forth main conclusion* of this project is that, **individuals with knee OA do not present excessive knee loading during more demanding tasks, such as step-up-and-over or stair negotiation.** As more demanding and the cause of the first knee pain signs (Hensor *et al.*, 2015), stair/steps activities were expected to result in more differences in KCF between individuals with knee OA and healthy subjects than those observed during gait. Instead, in individuals with knee OA, KCF was not significantly different from controls during step-up-and-over, even presenting reduced KCF during stair ascent and descent compared to controls. Given these reductions during stair negotiation, KCF, particularly medial KCF, were not increased compared to gait. This in contrast to the observations in healthy subjects. This is indicative that stair negotiation is indeed more demanding than gait and for this reason individuals with knee OA can only perform it using compensatory mechanisms, such as increased trunk flexion and lean, reduced stair walking speed or using step-by-step strategy as observed in the present study. Therefore, our project suggests that individuals with knee OA do not require the use of compensatory mechanisms during gait while they do to perform stair negotiation tasks.

The *fifth main conclusion* of this project is that **step-up-and-over cannot be used to mimic the functional stair walking activities to evaluate physical function (Dobson *et al.*, 2013) in individuals with knee OA**. Indeed, similar to stair ascent and descent, step-up-and-over requires an upward propulsive phase, compared to stair ascent, as well as a downward energy absorption phase (lowering phase) compared to stair descent.

However, as highly demanding and more difficult to be standardized, the step-over-step task causes a large variability in task performance between trials and subjects and, consequently, it limits the statistical power when evaluating differences in kinematics and loading patterns between groups. Although, in healthy subjects, step-up-and-over and stair negotiation resulted in similar KCF magnitudes, stair negotiation did not cause the high variation found during step-up-and-over. This probably due to its cyclic nature. Therefore, stair negotiation may result in differences between groups when assessing physical function while step-up-and-over does not.

6.4 Limitations

All results presented in the PhD have to be interpreted in view of certain methodological limitations related to the experimental protocols and to the musculoskeletal modeling approaches.

6.4.1 Experimental protocol

Firstly, errors in the experimental data collection such as errors due to **marker misplacement** that result in errors in kinematic parameters. In gait analysis, marker trajectories and ground recation forces are the input measurements used to estimate joint angles and moments. Therefore, the accuracy of any further processing is highly determined by the accuracy of the data collection. Ideally, reliability (repeatability or reproducibility) measurements of the gait analysis procedure should have been included in this manuscript, however these were not included in our studies. Based on previous literature (Kadaba *et al.*, 1989, Tsushima *et al.*, 2003) that assessed reproducibility in gait analysis, the coefficient of multiple correlation (R_{CMC}) for intra-subject (within-day) exceeded 0.90 for all movements except pelvic tilt ($0.50 < R_{CMC} < 0.70$) and the R_{CMC} for test-retest (between-days) exceeded 0.80 for all movements except pelvic tilt ($0.40 < R_{CMC} < 0.65$). However, attempts were made to minimize these errors: firstly, all data collection for the group 1 and 2 were performed by the same person, trying to minimize the random errors result from the experimenter's inability to take the same measurement in the way; secondly, by using three-marker cluster on the thigh and shank segments a redundant segment definition was obtained, since each cluster enables tracking of each segment independently and, therefore, maintained the accuracy even if some marker is missing; thirdly, in study II by using functional axes, which are less dependent on marker misplacement than the transepicondylar axis, in the knee joint definition. It is important to notice that, although functional methods are less dependent on those measurement errors, they are still sensitive to the type of the calibration motion, as demonstrated by using different motions as input in the functional algorithm, and also to soft tissue artefacts, i.e., the relative movement between markers and bone. Even though, since there was no significant difference in BMI between the groups, soft tissue artifacts may have affected the three groups similarly and, therefore, differences between groups did not likely result from these errors. In addition, in the same study, only the knee joint axis was determined based on functional approach. Hip and ankle joints preserved their positions and orientations with respect to the markers as defined in the generic model. Consequently, although a good fit was achieved for the tibia segment, any offset between the knee and ankle axis was not accounted for in our study. Therefore, since the definition of the ankle axis (in which only one DoF was considered) influences the knee kinematics (Reinbolt *et al.*, 2005), this could introduce some errors. Even though, marker errors calculated after inverse kinematics were similar for TEA and FAR models. Therefore, the introduction of a functional axis did not negatively affect the fit with the experimental data. In both study I and II, a 2-DoF knee joint model was used, including rotation in the sagittal and frontal planes but not in the transversal plane. The exclusion of the knee internal-external rotation was due to the marker set used during the data collection. Markers of the femur and tibia were found to be closely aligned with the longitudinal axis, which is the axis of rotation for the internal-external rotation. Consequently, any wobbling of the marker would inflate into a large change in the internal-external rotation. This is not an issue for the ab-adduction motion since the markers are further away from the abduction axis.

Secondly, patient's symptoms were not analysed in light of their psychological, social and cultural context. Therefore, any interpretation about self-reported complaints, particularly those collected by the questionnaires in terms of pain, functionality and general welfare might include some over- or underestimation of those assessed parameters. The inclusion of a biopsychosocial model (Engel, 1977) would be helpful in further understanding the impact of patient's life aspects on their reported sympthoms and feelings.

Thirdly, the number of participants in study IV was limited. Although a total number of eighteen participants (including ten healthy subjects and eight with knee OA) participated in the study, only five out of eight patients diagnosed with knee OA met the requirements of the inclusion criteria. A larger population-based study would provide more confident in-depth investigations by increasing the statistical power, i.e. the likelihood of deciding there is an effect, when one exist.

6.4.2 Musculoskeletal modeling

Firstly, limitations that are **inherent to the musculoskeletal models** used through the different studies. The OpenSim generic musculoskeletal lower body model (Delp *et al.*, 1990) was used in study I and II. The knee joint was modeled as a 2-DoF planar joint that only includes rotation motions in the sagittal and frontal planes, and the proximal-distal and anterior-posterior translations are defined as a function of the knee flexion adapted from the simplified knee model developed by Yamaguchi and Zajac (1989). Using this simplified model, only knee flexion and adduction were estimated based on the marker trajectories. Since translations were defined as a function of knee flexion, load-dependent variations in joint translations were ignored. Previous research showed that secondary tibiofemoral kinematics (anterior-posterior translation, internal-external rotation, and abduction-adduction) vary substantially over the gait cycle as a result of loading effects (Dyrby and Andriacchi, 2004). In addition, using this simple model we can only compute the total KCF and not the medial and lateral KCF. Furthermore, this model does not include ligaments assuming that external moments were generated entirely by the muscle-tendon structures. Ligaments have shown to provide significant resistance to the KAM immediately after heel strike and during midstance of gait (Shelburne et al., 2006) and, therefore, they would contribute to the KCF calculation. A more complex 12-DoF knee model was used in study II and IV. Different from the previous model, this model includes ligaments, articular cartilage that allows the computation of contact pressures. Furthermore, the secondary tibiofemoral kinematics (tibiofemoral translations and non-sagittal rotations) and patellofemoral kinematics are load-dependent as they evolve as a function of muscle and ligament forces, and cartilage contact. The validation of this model was done by comparing estimated knee kinematics (closed kinetic chain movement) with *in vivo* knee kinematics collected during supine posture tasks (open kinetic chain movement) by dynamic MRI (Lenhart *et al.*, 2015). In this model, the ligaments are represented as nonlinear spring elements, one-dimensional discrete elements, rather than deformable 3D representations that account for spatial variations in strain. Instead, some wrapping surfaces were included to improve wrapping around the bony structures but no ligament–ligament interactions were incorporated. The thickness of the cartilage surface was assumed constant, which is a simplification since cartilage thickness varies. This simplification might result in differences in terms of contact pressures and contact areas (Anderson *et al.*, 2010). Further, the knee model does not include menisci, which are known to distribute pressure in the tibiofemoral joint. Therefore, the absence of menisci might increase the peak contact pressures in the knee joint surface.

Secondly, **inclusion of subject-specific characteristics** into the knee models was limited. In all studies, generic models that were scaled to represent only the anthropometry of the subjects were used. Subject-specific articular geometries, muscle-tendon and ligaments properties (when ligaments were included) were not considered in our approaches since there was no data available for the cohort used. Therefore, the models do not account for OA induced changes in the articular geometry, such as thickness and mechanical properties of the cartilage, or changes in the muscle and ligament properties. Consequently, the reported differences in KCF and contact pressures only result from altered kinematic and kinetic behavior. Bone deformities, ligament laxity or changes in cartilage induced by joint degeneration were not taken in account and they might produce an effect on contact pressures (Smith *et al.*, 2015).

Thirdly, limitations resulted from the **static optimization techniques** used to calculate muscle forces. In optimization methods, the same cost function is assumed for both healthy and OA subjects. The static optimization routine available in OpenSim minimizes the sum of the muscle activations squared (minimal effort) and it was used in study I. The COMAK algorithm minimizes the weighted sum of squared muscle activations and the net cartilage contact elastic energy and was used in study III and IV. These cost functions are based on previous studies (Challis, 1997) that showed that the minimization of effort yields muscle activation patterns similar to those observed experimentally. However, it is unknown how much they represent the true muscle coordination strategy, especially, when the analyzed motion deviates from the normal walking pattern. Thus, the calculated muscle forces did not necessarily capture the effect of co-contraction patterns (Hubley-Kozey *et al.*, 2008), which may reduce the estimated knee loading. Furthermore, although computationally inexpensive, as an inverse dynamics problem, static optimization neglect muscle activation and contraction dynamics. However, static and dynamic optimization solutions have been proven to provide similar muscle forces during gait (Anderson *et al.*, 2001). Although COMAK uses a more accurate model, which accounts for load-dependency to calculate kinematics, some problems in trying to find an optimal solution were found for some subjects from study III that were not observed in study I, when OpenSim was used, and, therefore, they needed to be discarded from study III. COMAK uses gradient based optimization, so it is possible it gets caught in local minimums where it cannot find a set of muscle activations/secondary kinematics that satisfy dynamic equilibrium.

6.5 Future Perspectives

Inclusion of muscle co-contraction by using EMG driven simulations

In this project, muscle forces were calculated using a static optimization approach. This approach determines the muscle forces that produce the inverse dynamics joint moments by minimizing a cost function (more specific by minimizing the sum of squared muscle activations – study I; by minimizing the muscle volume weighted sum of squared muscle activations plus the net knee contact energy – study III and IV). Although static optimization has shown satisfactory results in calculating muscle forces during gait, studies have shown that individuals with knee OA exhibit different muscle activation patterns compared to healthy subjects (Childs *et al.*, 2004; Hubley-Kozey *et al.*, 2008; Lewek *et al.*, 2004; Heiden *et al.*, 2009; Zeni *et al.*, 2010). High muscle co-contraction has been observed in OA patients that might result in higher joint loading (Hubley-Kozey *et al.*, 2008; Schmitt and Rudolph, 2008). Using static optimization, these co-contraction patterns are not accounted for. Recent studies (Winby *et al.*, 2009; Winby *et al.*, 2013; Kumar *et al.*, 2012) reported significant correlations between specific activity patterns (as measured by EMG sensors) and the articular loading (Winby *et al.*, 2009; Winby *et al.*, 2013) when using an EMG-driven model to calculate individual muscle forces and tibiofemoral contact forces in healthy individuals during gait. Since muscle forces are the main contributors to joint contact forces, muscle coordination strategy is expected to highly influence joint contact loading. Therefore, the inclusion of individual muscle force activity in the muscle force and consequent tibiofemoral contact forces calculations in subjects suffering from knee OA during gait and also during more strenuous activities such as stair negotiation, must be the next step.

EMG-constrained static optimization can improve muscle force estimation by matching the muscle activity patterns collected from EMG-sensors. To include muscle co-contraction as derived from surface EMG recordings, the cost function can be extended with an additional term penalizing the difference between the simulated and measured activity patterns or some constraints can be added. These constrains are derived from EMG recording collected from the knee extrinsic muscles in order to constrain the solution space of available solutions throughout the gait cycle. Since EMG signals were collected for the different studies, it would be possible to use EMG-constrained static optimization to evaluate contact loading during gait and step-up-and-over in healthy subjects and patients with early and established medial knee OA (data of Study III), as well as during stair negotiation strategies in healthy subjects and patients with medial knee OA (data of Study IV) in a follow-up study.

Inclusion of subject-specific characteristics into the knee models

In all studies in this manuscript, scaled generic models only representative for the anthropometry of the subjects were used. However, joint loading can be affected by joint geometry, mechanical properties of the cartilage and bone, muscle strength/weakness and ligament properties, which are likely altered in individuals with knee OA (Bhatia *et al.*, 2013; Liikivainio *et al.*, 2008; Andriacchi *et al.*, 2004). Therefore, the importance of subject-specific geometric characteristics in the musculoskeletal models used to calculate knee loading has been questioned. A recent study conducted in one subject with instrumented TKA by Gerus *et al.* (2013) shows that inclusion of the subject-specific knee joint geometry improves the accuracy of the estimated medial KCF over the generic model. However, this was only on the condition that also muscle-tendon parameters are adjusted so that peak KCF is minimized during the calibration. Indeed, by changing the generic to a subject-specific geometry, moment arms and forces of the muscles surrounding the knee are affected due to changes in the muscle-tendon paths and in the knee joint centre position. Consequently, the muscle-tendon paths need to be adjusted based on medical imaging (e.g. MRI and/or ultrasonography). Another study conducted on five healthy subjects has shown that the inclusion of the MRI-based subject-specific geometrical detail widely affected the hip contact forces (Wesseling *et al.*, 2016). In addition, it is well-known that patients with OA complain of muscle weakness (Bhatia *et al.*, 2013; Likivainio *et al.*, 2008), which might have an effect on calculated muscle forces and, ultimately, on the resulting knee contact forces. Therefore, a measurement of muscle strength examined by dynamometry might also be considered to scale to maximum force of the muscle-tendon structures of the musculoskeletal model. Finally, it is known that forces in the ligaments can vary significantly between individuals due to subject specific gait characteristics and knee joint geometries (Morrison *et al.*, 1970). This is also relevant for individuals with knee OA, who commonly present increased passive knee laxity (Lewek *et al.*, 2004). Therefore, further investigation is recommended to better understand the importance of having a subject-specific model in estimating KCF on the knee joint for individuals with knee OA.

To adequately include the subject-specific articular geometries and adjust each muscle-tendon paths, MRI scanning has to be performed and subject-specific 3D musculoskeletal models have to be created. However, although MRI was used to evaluate knee OA severity, the MRI images did not include the entire lower limb and only focus on the tibiofemoral and patellofemoral articular joints. Consequently, the muscle origins and insertions cannot be assessed. Furthermore, together with MRI scans, laxity tests as well as dynamometry measurements are needed to assess, respectively, the ligament properties and the muscle strength, and these tests were not performed for this cohort. Therefore, current OA repositories do not include the information to make subject-specific models that include subject-specific joint, ligament and muscle characteristics. For future work, in order to improve the model definition, subjects are recommended to undergo full lower body MRI scans and laxity tests are suggested measures.

Assessment of the unloading effect of the valgus brace on the knee loading in patients with medial knee OA during stair negotiation

Valgus braces have been used in medial knee OA patients to unload the medial compartment. Potential mechanisms by which a valgus brace alters knee loading are the application of a valgus moment at the knee directly opposing the external KAM, with or without altering the frontal plane alignment. Previous studies have reported contradicting results on the effect of unloading knee braces on knee loading (Moyer *et al.*, 2015), which might be influenced by the brace type. Some studies reported significantly decreased KAM while wearing a valgus knee brace during gait (Pollo and Jackson, 2006; Pagani *et al.*, 2010). However, others did not find any effect on the KAM (Schmalz *et al.,* 2010) but only on the net knee joint moment (Pollo *et al.*, 2002). Decreased muscle co-contraction (Pagani *et al.*, 2013; Ramsey *et al.*, 2007), increased joint stability (Childs *et al.*, 2004; Hortobagyi *et al.*, 2005), and also increased medial joint space (Dennis *et al.,* 2006) as a result of wearing a valgus brace have been reported during gait. To date, no studies have investigated the effect of valgus bracing on knee loading in terms of contact forces and/or contact pressures. This is particularly relevant as the brace might affect not only the frontal plane mechanics (Pollo and Jackson, 2006; Pagani *et al.*, 2010), but also knee stability (Childs *et al.*, 2004; Hortobagyi *et al.*, 2005) and muscle coordination (Pagani *et al.*, 2013; Ramsey *et al.*, 2007). Therefore, the first objective is to evaluate the unloading effect of the valgus brace on the knee contact forces and contact pressures in OA subjects during stair negotiation. The second objective is to assess the effect of the valgus brace on joint space width demonstrated in weight-bearing MRI. We hypothesize that a valgus brace will reduce medial compartment knee loading especially in those patients presenting increased joint space measures during the standing MRI when wearing the brace.

Methods

Three-dimensional marker trajectories and GRF were also collected during stair negotiation tasks in five individuals with medial knee OA wearing a knee valgus brace, i.e. the unloader OA knee bracing by Ossur. Furthermore, patients underwent standing MRI for both conditions: before and while wearing the valgus brace.

Firstly, KCF and contact pressure will be calculated during stair ascent and descent in patients wearing the valgus brace using different strategies: step-over-step at constant/controlled speed and step-by-step. Secondly, the 3D joint space morphology with and without brace will be characterized.

To include the external forces provided by the valgus brace into the knee model, the brace moment has to be calculated. Previous studies have measured the brace moment in instrumented braces (Self *et al.* 2000; Pollo et al. 2002; Fantini Pagani *et al.* 2010; LaPrada *et al.* 2015) or, instead, using a linear stiffness model to relate measured deflection to moment (Kutzner *et al.* 2011; Schmalz *et al.* 2010). While the first approaches offer more direct measurements, the latter method might be more comfortable for patients and therefore has less collateral effect on their locomotion. Since no instrumented brace was available, the second approach will be chosen. However, this approach requires some assumptions that need to be tested first.

Preliminary results

One example data set in one OA patient is presented. When wearing the brace, the subject with medial knee OA clearly reduced the RoM in the three planes of motion during both stair ascent (Figure 6.3) and descent (Figure 6.4).

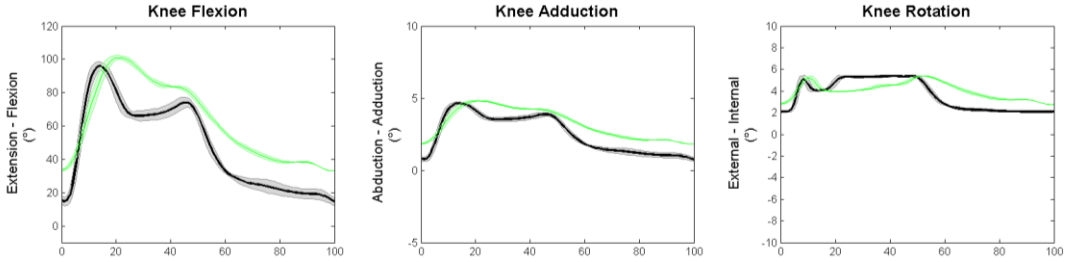

Figure 6. 1 - Knee flexion, varus-valgus and rotation angles before (black line) and after (green line) wearing the valgus brace on while ascending stairs during the entire gait cycle.

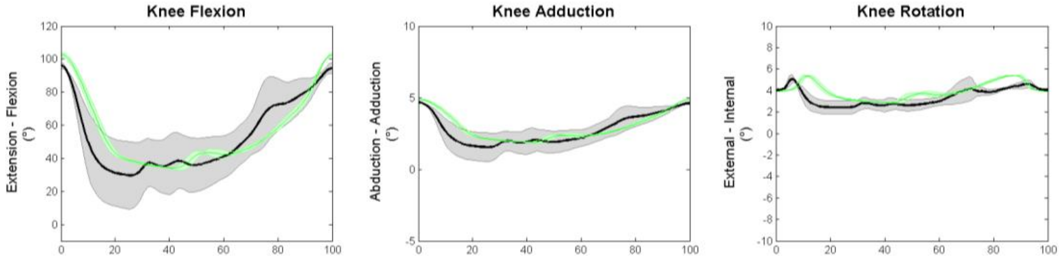

Figure 6. 2 - Knee flexion, varus-valgus and rotation angles before (black line) and after (green line) wearing the valgus brace on while descending stairs during the entire gait cycle.

Preliminary conclusions

The brace constrained the knee extension, valgus and external rotation. Furthermore, during stair descent, a lower variation between the trials was found, suggesting that the brace could at least provide a higher level of confidence and, ultimately, higher joint stability to the patients.

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Appendices

Appendix A

Part A.1. Testing functional calibration methods

Purpose

We evaluated three methods for estimating the functional axis of a joint with one or two degrees of motion (DoF) based on synthetic marker data and selected the method that performed best for a 2-DoF knee joint. We excluded methods that could not be applied *a posteriori* and methods using minimization of the variance in the abduction/adduction kinematic profile (e.g. the method proposed by Rivest *et al*. (2005) or Schache *et al*. (2006), which was based on the DynaKAD method proposed by Baker *et al*. (1999) or methods that zeroed abduction/adduction rotation at the time of maximum knee flexion as proposed by Woltring *et al*. (1994). Such methods may be appropriate for healthy subjects but would hide existing mechanisms of pathological joints, as osteoarthritic knees that are often characterized by excessive frontal plane motion.

Based on these criteria, three methods were selected for an *a posteriori* analysis, each method being based on a different mathematical approach: (1) the fitting approach proposed by Gamage and Lasenby (2002) that was considered the best performing sphere fitting algorithm for a single DoF joint by MacWilliams (2008); (2) the axis transformation technique (ATT or SARA) by Ehrig *et al*. (2007), who found that the SARA method is the best performing axis transformation algorithm to estimate the position and orientation of an ideal hinge and (3) the geometrical approach proposed by Chang and Pollard (2007) that is similar to the method of Gamage and Lasenby (2002), but that minimizes the error along the axis of rotation (AoR) direction as well as the error orthogonal to the AoR direction. Therefore, this method is recommended for joints that exhibit a secondary rotational motion that is less than 50% of the dominant rotation (Chang and Pollard, 2007).

In the presented analysis, the performance of the geometrical algorithm is therefore compared to two other methods designed to estimate the axis of rotation for a 1-DoF rotational joint and that have already been shown to outperform other similar methods (Passmore and Sangeux, 2016). The geometrical method is expected to outperform the other methods for joints motions with two rotational degrees of freedom, since it was designed for this purpose.

Methods

The three methods were used to estimate the knee flexion axis from synthetically generated marker trajectories that were created from a known input joint motion and a known AoR for either one or two DoF (see Figure A.1). We generated marker trajectories for a gait cycle with and without noise. Synthetic data for the following markers: a tight cluster with three markers, markers on the medial and lateral epicondyles, a shank cluster with three markers, and markers on the medial and lateral malleoli. Numerical noise drawn from random numbers from normal distribution with an amplitude of 1 cm was added to the synthetic marker data to simulate measurement noise.

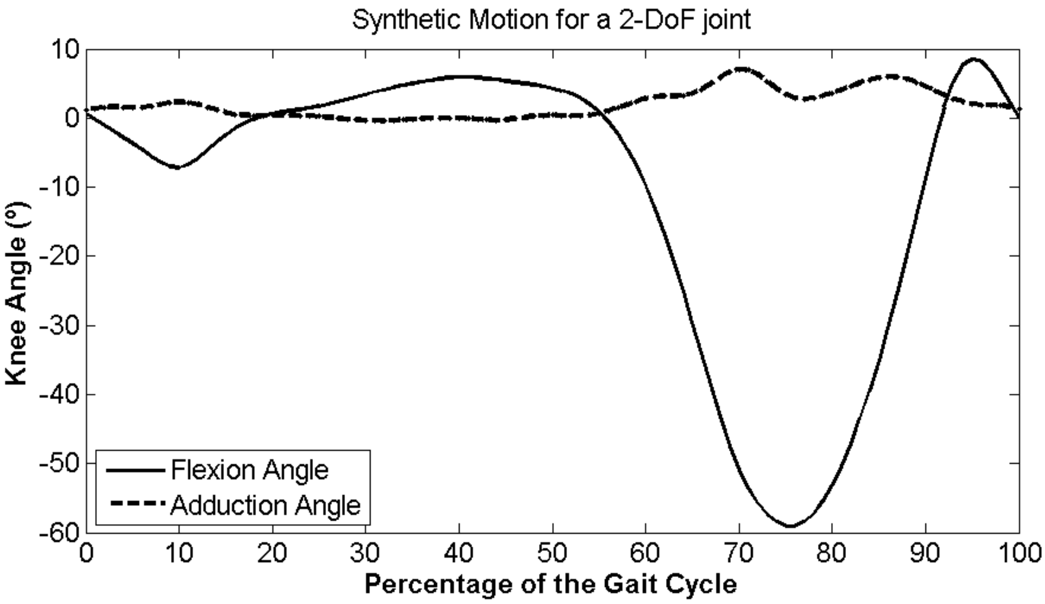

Figure A. 1 - Synthetic motion for a gait cycle generated for a 2-DoF knee joint. Knee flexion (negative) and adduction angles (positive) are presented.

Results and Discussion

Table A.1 and Table A.2 present the differences between the estimated orientation and position of the AoR estimated by the different algorithms and the known orientation and position of the AoR used to generate the synthetic motion. These differences were calculated for the three orientations (X, Y and Z), described by roll-pitch-yaw Euler angles, and the three positions (X, Y and Z) expressed in *cm* with respect to the femur and tibia, respectively. The performance of all three algorithms was lower for a motion along two DoF than for a motion along a single DoF. Nevertheless, the SARA method (Ehrig *et al*., 2007) was more accurate than the other two methods for either one or two DoF, with noise or without.

Table A. 1 - Differences in estimated orientation and position of the FAR and the modeled orientation and position of the AoR. Orientation is described by roll-pitch-yaw Euler angles with respect to the femur reference frame. Position of the axis is expressed in the XY-plane of the femur reference frame. Results are shown for the three methods analyzed in this study, for a motion along a single DoF and a motion along two DoF joint and for the marker trajectories without and with noise.

FEMUR

		Difference in Orientation			Difference in Position [cm]		
		X	Y	Z	X	Y	Z
1DoF	**Fitting (Fit)**	0.0002	0.0010	0.0001	0.011	0.020	0.000
	Fit w/ noise	0.0662	0.0281	0.0106	1.480	0.700	0.000
	SARA	***0.0000***	***0.0000***	***0.0000***	***0.010***	***0.010***	***0.000***
	SARA w/ noise	***0.0095***	***0.0568***	***0.0091***	***0.404***	***0.500***	***0.000***
	Geometrical (Geo)	0.0002	0.0009	0.0001	0.010	0.010	0.000
	Geo w/ noise	0.0830	0.1532	0.0400	0.350	0.720	0.000
2DoF	**Fitting (Fit)**	0.1282	0.1973	0.0041	0.010	0.010	0.000
	Fit w/ noise	0.0828	0.1507	0.0275	0.790	0.390	0.000
	SARA	***0.0680***	***0.0566***	***0.0074***	***0.000***	***0.010***	***0.000***
	SARA w/ noise	***0.0405***	***0.0048***	***0.0013***	***0.230***	***0.160***	***0.000***
	Geometrical (Geo)	0.1161	0.1663	0.0068	0.010	0.010	0.000
	Geo w/ noise	0.0572	0.0790	0.0103	0.130	0.640	0.000

Table A. 2 - Differences in estimated orientation and position of the FAR and the modeled orientation and position of the AoR. Orientation is described by roll-pitch-yaw Euler angles with respect to the tibia reference frame. Position of the axis is expressed in the XY-plane of the tibia reference frame. Results are shown for the three methods analyzed in this study, for a motion along a single DoF and a motion along two DoF joint and for the marker trajectories without and with noise.

TIBIA

		Difference in Orientation			**Difference in Position [cm]**		
		X	**Y**	**Z**	**X**	**Y**	**Z**
1DoF	**Fitting (Fit)**	0.0002	0.0007	0.0001	0.012	0.010	0.000
	Fit w/ noise	0.0789	0.2804	0.0075	0.984	0.495	0.000
	SARA	***0.0005***	***0.0003***	***0.0001***	***0.010***	***0.010***	***0.000***
	SARA w/ noise	***0.0031***	***0.0509***	***0.0039***	***0.322***	***0.100***	***0.000***
	Geometrical (Geo)	***0.0002***	0.1846	0.0001	0.030	0.030	0.000
	Geo w/ noise	0.0458	0.4575	0.0604	0.270	0.430	0.000
2DoF	**Fitting (Fit)**	0.0961	0.0499	0.0123	0.004	0.020	0.000
	Fit w/ noise	0.0626	0.3118	0.0294	0.622	0.260	0.000
	SARA	***0.0712***	***0.0336***	***0.0145***	***0.010***	***0.002***	***0.000***
	SARA w/ noise	***0.0576***	***0.0240***	***0.0024***	***0.365***	***0.106***	***0.000***
	Geometrical (Geo)	0.1754	0.2148	0.0395	0.030	0.070	0.000
	Geo w/ noise	0.1203	0.6472	0.1901	1.310	1.370	0.000

Part A.2. Comparing the effect of different functional tasks to calculate the functional axis

Purpose

In the main manuscript we report the effect of calculating FAR based on weight-bearing or non-weight-bearing motion on KAM. Although different motions can be selected as representative for weight-bearing or non-weight-bearing, the appropriateness of the different motions for the calculation of FAR was evaluated (Ehrig *et al*., 2007). Therefore, five different motions were used to calculate the FAR using the SARA method in control subjects. The effect of the calculated FAR using different motions on KAM was evaluated.

Motions

Stance phase of gait motion (3 to 6 trials), stance phase of step-up motion (3 trials), sit-to-stand-to-sit motion (3 to 6 trials) were used as weight-bearing motions. Swing phase of step-up-and-over motion and dynamic motion (3 trials), which is the active flexion-extension of the unloaded tibia with the femur kept stationary, were used as non-weight bearing motions (Table A.3). Each of these movements were evaluated in terms of four characteristics that potentially can affect the calculation of the functional axis of rotation, more specific (1) differences in number of frames, with a higher number of frames resulting in a more accurate definition of segmental rotation; (2) range of motion (RoM), with lower RoM resulting in less representative FAR (Ehrig *et al*., 2007); (3) movement scenario in terms of one stationary and one moving segment or two moving segments and (4) presence of in or out of plane movement of the markers during the motion (Table A.3). More demanding weight-bearing motions such as squat (similar to sit-to-stand-to-sit) have shown to have a high incidence in causing medial knee displacement (valgus knee collapse) (Bell *et al*., 2008; Hirth, 2007; Hole, 2013; Kritz et al., 2009; Padua et al., 2012). This out of plane motion during sit-to-stand-to–sit was confirmed by calculating the root-mean-square distance (RMSD) of the femur markers to the planes that best explained the motion of 3 femur markers relative to the tibia throughout the frames. This was calculated and compared between the stance phase of step-up motion and sit-to-stand-to-sit motion. RMSD were calculated for all subjects (20 subjects with asymptomatic healthy knees, 16 patients with early knee OA and 23 patients with established OA) of the 3 groups and *t-test* performed to determine whether the average error was significantly higher ($p < 0.05$) in sit-to-stand motion compared stance phase of step-up.

Results and Discussion

Swing phase of step-up-and–over and dynamic motion (both non-weight bearing and closely planar motions) resulted similar KAM (Table A.4 and Figure A.2). This confirms the ability of SARA method (Ehrig *et al*., 2007) in considering two moving body segments simultaneously. Although both present different number of frames and different RoM, both produced similar results. This suggests that these characteristics did not affect the calculated KAM (at least for a minimum of RoM of 60º, regarding to the comparison in terms of RoM).

Stance phase of gait and stance phase of step-up motion (both weight-bearing motions, same movement scenario and type of motion) produced significantly different 2nd peak KAM ($p = 0.038$). The observed differences during stance phase of gait suggest that lower RoM and/or differences in the ROM (reduced knee flexion during gait as compared to step-up) significantly influences the FAR calculation and, consequently, the KAM.

Stance phase of step-up and sit-to-stand-to-sit (both weight-bearing motions, however, the first one is "closely planar" while the second one is "less planar") induced significant different KAM ($p < 0.001$). For the stance phase of step-up motion, the following averaged RMSD with the respective standard deviation (SD) were obtained: 0.0212±0.0051*mm,* 0.0200±0.0040*mm* and 0.0227±0.0058*mm* for control, early OA and established OA respectively. For the sit-to-stand-to-sit motion, the following averaged RMSD with the respective SD were obtained: 0.0291±0.0081 *mm;* 0.0287±0.0069*mm* and 0.0344±0.0117*mm* for control, early OA and established OA respectively. RMSDs were significantly ($p < 0.0001$) higher for the sit-to-stand-to-sit motion compared to the stance phase of step-up motion. Therefore, sit-to-stand-to-sit was characterized as a "less planar" motion. These findings then showed that the type of motion ("less planar motion") did significantly influence KAM calculations.

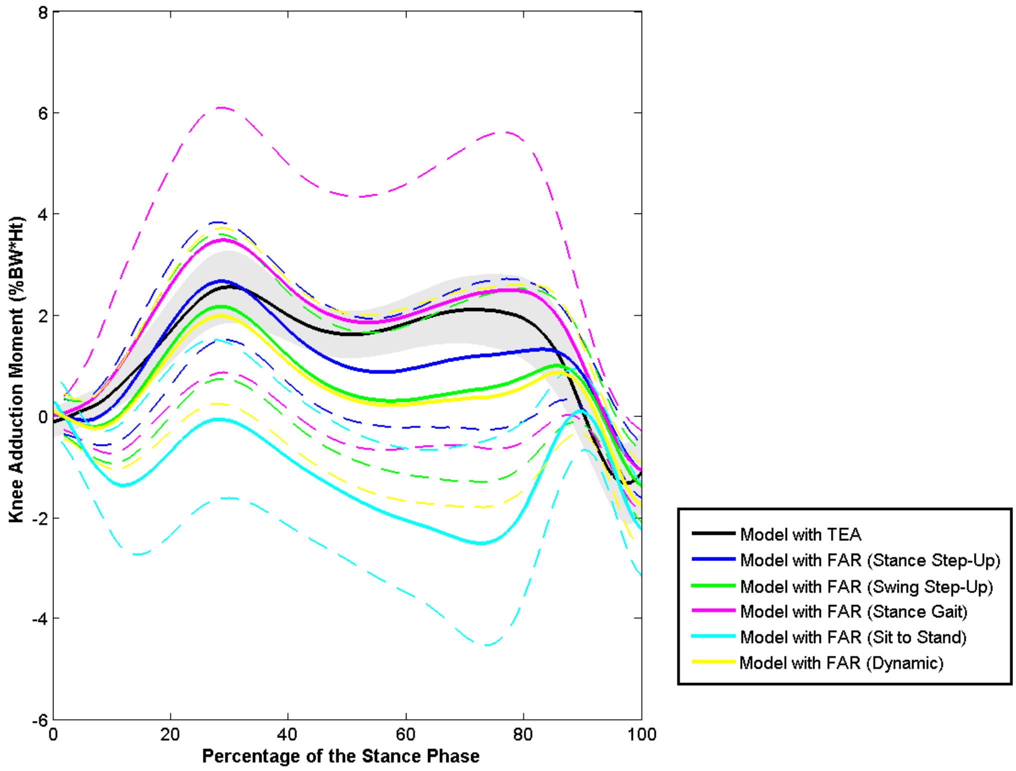

Figure A. 2 - Mean knee moments in the frontal plane for the TEA (solid black line), FAR using 5 different motions: stFAR (solid blue line); swFAR (solid green line); gFAR (solid pink line); sFAR (solid light blue line); and, dFAR (solid yellow line). The grey shaded area and the areas between thin dashed lines indicate standard deviation of the respective FAR model.

Table A. 3 - Characteristics of the motion used to calculate FAR by SARA method.

MOTION	No. of frames	Min & Max Flexion Angles (º)	RoM (º)	Movement Scenario	Type of Motion
Stance of Gait (weight-bearing)	80	~ (10-40)	~30	2 moving segments	Closely planar motion
Stance of Step-Up (weight-bearing)	150	~ (40-110)	~70	2 moving segments	Closely planar motion
Sit-to-Stand-to-Sit (weight-bearing)	1300	~ (10-130)	~100	moving femur stationary tibia	Less planar motion
Swing of Step-up-and–over (non-weight bearing)	150	~ (0-100)	~120	2 moving segments	Closely planar motion
Dynamic motion (non-weight bearing)	600	~ (10-70)	~60	moving tibia stationary femur	Closely planar motion

Passmore and Sangeux (2016) already reported similar differences in the orientation of the AoR when using different calibration motions (squat, flexion-extension and walk) to calculate the FAR using either a transformation technique (SARA method) (Ehrig *et al*., 2007) or a geometrical method (Chang and Pollard, 2007). Likewise, they found the worst results when using a squat motion (which is similar to stand-to-sit motion presented in our study) as input motion to calculate functional axis based on either methods. FARs obtained from squat motions, while using the SARA or geometrical methods, differed more in orientation from the 3D-ultrasound reference frontal plane axis compared to walk or flexion-extension motions (Passmore and Sangeux, 2016). Although they found good results using walking trials to calibrate the FAR, this was not confirmed in the present study. However, a comparison of the results is not straightforward. Whereas the current study the knee joint only accounts for 2 DOF, their model allowed rotation along 3 DoF. Furthermore, in the current study, only the stance phase of gait was included to calculate the FAR. Whereas they used the entire gait cycle as calibration trial.

Conclusion

For the weight-bearing motions, stance phase of gait had insufficient RoM and sit-to-stand-to-sit motion showed to be less planar resulting in significant different KAM. Therefore, stance phase of step-up motion was selected as the weight-bearing motion to be used for the analysis of the different groups in the main manuscript. For the non-weight-bearing condition, both swing phase of step-up-and-over motion or dynamic motion were found to be appropriate, and then the swing phase of step-up-and-over motion was selected.

Table A. 4 - Peak values of the KAM during stance phase of the gait cycle for the modified models: FAR calculated from weight-bearing motions such as stance of the step-up motion (stFAR); FAR from stance of gait (gFAR); FAR from sit-to-stand-to-sit (sFAR); and FAR calculated from non-weight bearing motions such as swing of the step-up-and–over motion FAR (swFAR) and dynamic motion (dFAR) for healthy subjects.

External Moments		**Stance Step-Up (stFAR)**	**Stance Gait FAR (gFAR)**	**Sit to Stand FAR (sFAR)**	**Swing Step-Up (swFAR)**	**Dynamic Motion FAR (dFAR)**	***p* (stFAR vs gFAR)**	***p* (stFAR vs sFAR)**	***p* (stFAR vs swFAR)**	***p* (stFAR vs dFAR)**	***p* (swFAR vs dFAR)**
KAM	**P1**	2.70±1.17	3.52±2.59	0.03±1.49	2.20±1.42	2.01±1.75	*0.149*	***<u>0.000</u>***	*0.130*	*0.162*	*0.720*
	P2	1.59±1.18	2.86±2.72	0.21±0.74	1.31±1.33	1.24±1.63	***<u>0.038</u>***	***<u>0.000</u>***	*0.322*	*0.441*	*0.871*

KAM expressed as mean ± SD (%BW*Ht), where SD is standard deviation.
P1 and P2 correspond, respectively, to first and second peak values.
P values **<u>in bold and underlined</u>** indicate a significant difference (*p* < 0.05 or 0.001) from paired t-test between the different modified models.

Part A.3. Orientation of the Functional Axis calculated during weight-bearing versus non-weight bearing motion

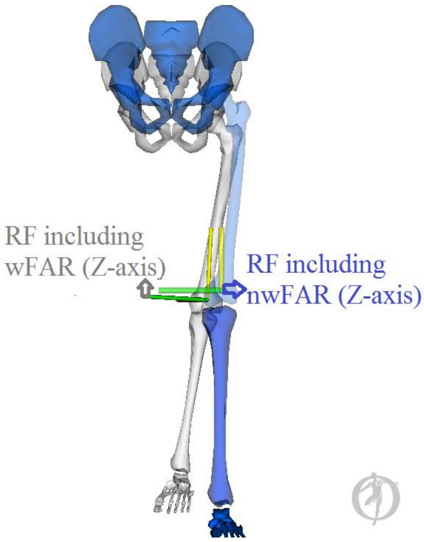

Figure A. 3 - Left knee model of one subject as an example obtained from wFAR (gray model) and nwFAR (blue model) calculations, including the reference frame obtained from FAR calculation with respect to the femur.

Table A. 5 - Comparison of the orientation (°) between the wFAR and the nwFAR model. Mean absolute differences for the orientation about the anterior-posterior axis, corresponding to the abduction-adduction rotation axis, between the two FAR models are presented in degrees and standard deviations are reported between brackets.

	Mean absolute difference in axis orientation (deg.)
	Abduction-adduction axis
Control	0.99 (±4.54)
p-value	*0.149*
Early OA	1.70(±4.76)
p-value	*0.102*
Established OA	**2.30(±5.10)***
p-value	***0.015***

* Significant difference $p < 0.05$ from Wilcoxon matched-pair test.
Positive values correspond to adduction orientations.

Part A.4. Bland and Altman plots for assessing the agreement between the models

Bland and Altman plots for first and second peak KAM of control, early OA and established OA groups obtained from comparison between TEA models and wFAR models, and TEA models and nwFAR models. The plots represent the peak differences between TEA and FAR models (wFAR and nwFAR, separately) *versus* the mean of the peaks of KAM obtained from the two models. The average difference between the peak moments is represented by the red lines (bias) and the limits of agreement are represented by the green lines (from -1.96SD to +1.96SD, corresponding to a 95% confidence interval, where SD is the Standard Deviation). The plots include also the representation of confidence interval limits for mean and agreement limits in dotted lines with the respective color. All the numerical values and elements to calculate confidence intervals are presented in the Table A.6.

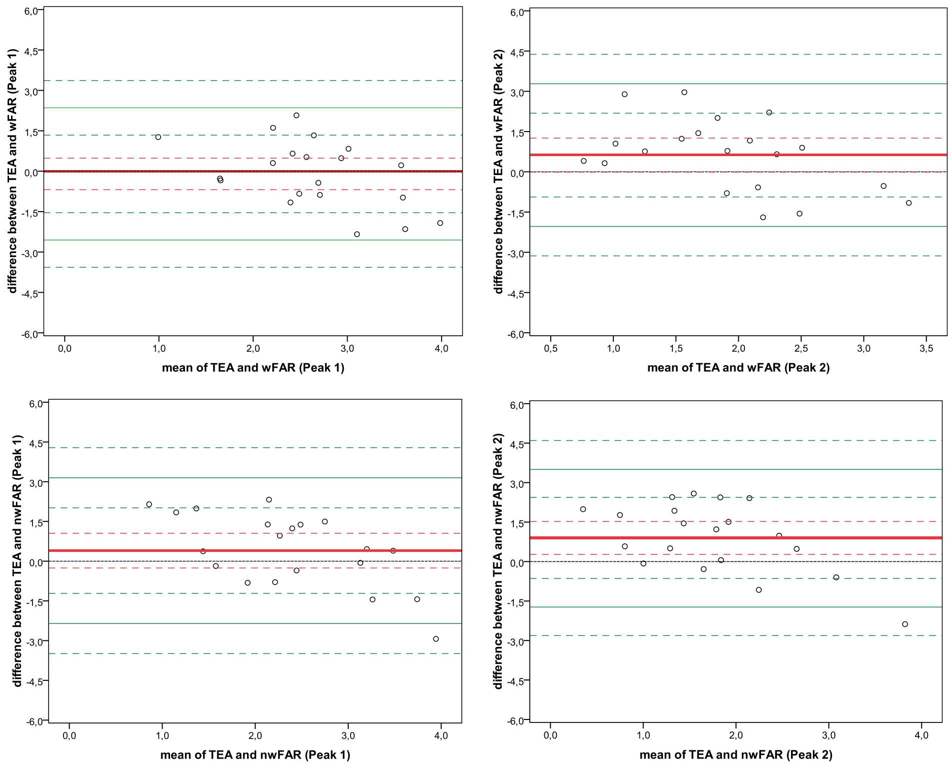

Figure A. 4 – TEA models versus wFAR models (upper row) and TEA models versus nwFAR models (lower row), 1st peak (on the left) and 2nd peak (on the right) for the control group.

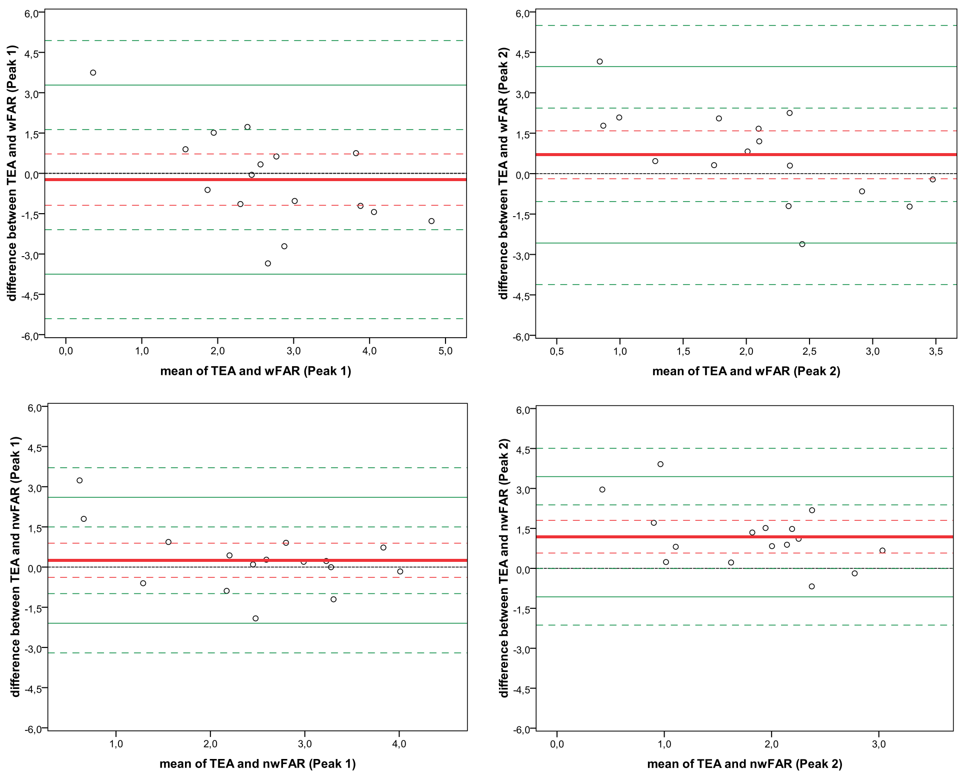

Figure A. 5 - TEA models versus wFAR models (upper row) and TEA models versus nwFAR models (lower row), 1st peak (on the left) and 2nd peak (on the right) for the early OA group.

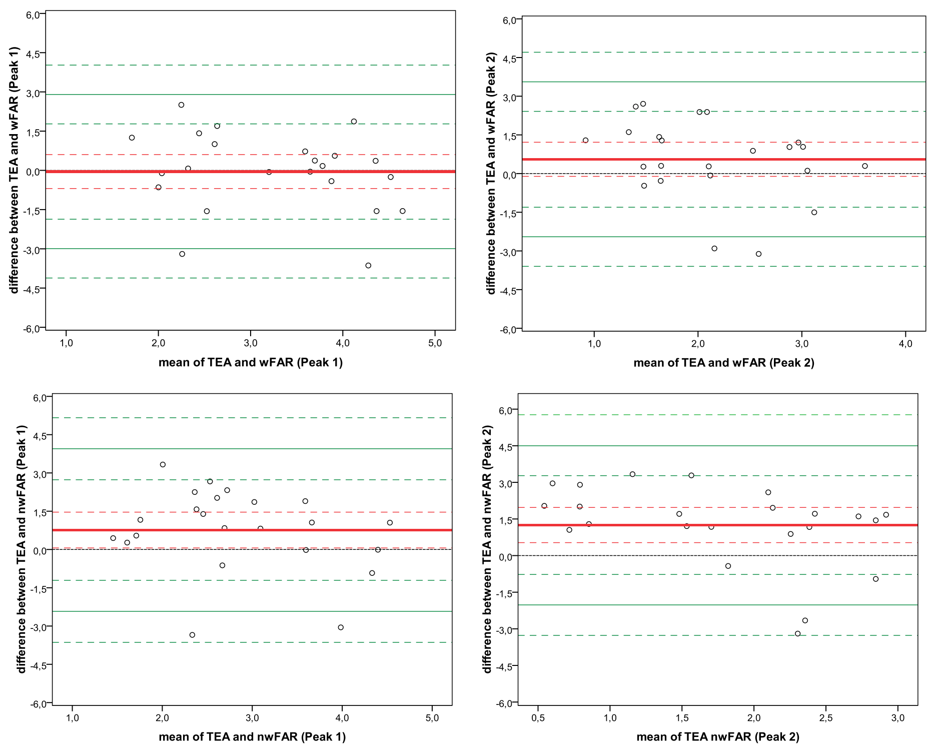

Figure A. 6 - TEA models versus wFAR models (upper row) and TEA models versus nwFAR models (lower row), 1st peak (on the left) and 2nd peak (on the right) for the established OA group.

Table A. 6 - Bland and Altman plot statistics for comparing the agreement between TEA vs. wFAR models, and TEA vs. nwFAR models at the first and second peak KAMs.

			Parameter	Unit	Standard error formula	Standard error (SE)	t value for 19 degrees of freedom	Confidence (SE*t)	Confidence intervals from	Confidence intervals to
CONTROL			number (n)	20						
			degrees of freedom (n-1)	19						
	TEA *vs.* wFAR	**P1**	difference mean (d)	**-0.1009**	√(SD^2/n)	0.2800	2.09	0.5852	**-0.6861**	**0.4843**
			Standard Deviation (SD)	1.2521						
			d-1.96*SD	**-2.5550**	√(3*SD^2/n)	0.4849	2.09	1.0135	-3.5685	-1.5415
			d+1.96*SD	**2.3532**	√(3*SD^2/n)	0.4849	2.09	1.0135	1.3397	3.3667
		P2	difference mean (d)	**0.6232**	√(SD^2/n)	0.3034	2.09	0.6340	**-0.0108**	**1.2572**
			Standard Deviation (SD)	1.3567						
			d-1.96*SD	**-2.0359**	√(3*SD^2/n)	0.5254	2.09	1.0982	-3.1341	-0.9377
			d+1.96*SD	**3.2823**	√(3*SD^2/n)	0.5254	2.09	1.0982	2.1841	4.3805
	TEA *vs.* nwFAR	**P1**	difference mean (d)	**0.3983**	√(SD^2/n)	0.3138	2.09	0.6559	**-0.2576**	**1.0542**
			Standard Deviation (SD)	1.4035						
			d-1.96*SD	**-2.3526**	√(3*SD^2/n)	0.5436	2.09	1.1361	-3.4886	-1.2165
			d+1.96*SD	**3.1492**	√(3*SD^2/n)	0.5436	2.09	1.1361	2.0131	4.2852
		P2	difference mean (d)	**0.8971**	√(SD^2/n)	0.2995	2.09	0.6260	**0.2711**	**1.5231**
			Standard Deviation (SD)	1.3394						
			d-1.96*SD	**-1.7281**	√(3*SD^2/n)	0.5187	2.09	1.0842	-2.8123	-0.6439
			d+1.96*SD	**3.5223**	√(3*SD^2/n)	0.5187	2.09	1.0842	2.4381	4.6065
EARLY OA	**TEA *vs.* wFAR**		number (n)	16						
			degrees of freedom (n-1)	15						
		P1	difference mean (d)	**-0.2334**	√(SD^2/n)	0.4486	2.13	0.9556	**-1.1890**	**0.7222**
			Standard Deviation (SD)	1.7945						

			d-1.96*SD	**-3.7506**	√(3*SD^2/n)	0.7770	2.13	1.6551	-5.4057	-2.0955
			d+1.96*SD	**3.2838**	√(3*SD^2/n)	0.7770	2.13	1.6551	1.6287	4.9389
		P2	difference mean (d)	**0.6983**	√(SD^2/n)	0.4176	2.13	0.8894	**-0.1911**	**1.5877**
			Standard Deviation (SD)	1.6702						
			d-1.96*SD	**-2.5753**	√(3*SD^2/n)	0.7232	2.13	1.5405	-4.1157	-1.0348
			d+1.96*SD	**3.9719**	√(3*SD^2/n)	0.7232	2.13	1.5405	2.4314	5.5123
	TEA *vs.* nwFAR	**P1**	difference mean (d)	**0.2539**	√(SD^2/n)	0.2998	2.13	0.6385	**-0.3846**	**0.8924**
			Standard Deviation (SD)	1.1990						
			d-1.96*SD	**-2.0961**	√(3*SD^2/n)	0.5192	2.13	1.1059	-3.2020	-0.9903
			d+1.96*SD	**2.6039**	√(3*SD^2/n)	0.5192	2.13	1.1059	1.4981	3.7098
		P2	difference mean (d)	**1.1880**	√(SD^2/n)	0.2879	2.13	0.6131	**0.5749**	**1.8011**
			Standard Deviation (SD)	1.1514						
			d-1.96*SD	**-1.0687**	√(3*SD^2/n)	0.4986	2.13	1.0620	-2.1307	-0.0068
			d+1.96*SD	**3.4447**	√(3*SD^2/n)	0.4986	2.13	1.0620	2.3828	4.5067
ESTABLISHED OA			number (n)	23						
			degrees of freedom (n-1)	22						
	TEA *vs.* wFAR	**P1**	difference mean (d)	**-0.0453**	√(SD^2/n)	0.3135	2.07	0.6489	**-0.6942**	**0.6036**
			Standard Deviation (SD)	1.5033						
			d-1.96*SD	**-2.9918**	√(3*SD^2/n)	0.5429	2.07	1.1239	-4.1156	-1.8679
			d+1.96*SD	**2.9012**	√(3*SD^2/n)	0.5429	2.07	1.1239	1.7773	4.0250
		P2	difference mean (d)	**0.5533**	√(SD^2/n)	0.3197	2.07	0.6619	**-0.1086**	**1.2152**
			Standard Deviation (SD)	1.5334						
			d-1.96*SD	**-2.4522**	√(3*SD^2/n)	0.5538	2.07	1.1464	-3.5985	-1.3058
			d+1.96*SD	**3.5588**	√(3*SD^2/n)	0.5538	2.07	1.1464	2.4124	4.7051
	TEA *vs.* nwFAR	**P1**	difference mean (d)	**0.7626**	√(s^2/n)	0.3390	2.07	0.7016	**0.0610**	**1.4642**
			Standard Deviation (SD)	1.6256						
			d-1.96*SD	**-2.4236**	√(3*s^2/n)	0.5871	2.07	1.2153	-3.6389	-1.2083
			d+1.96*SD	**3.9488**	√(3*s^2/n)	0.5871	2.07	1.2153	2.7335	5.1641
		P2	difference mean (d)	**1.2513**	√(s^2/n)	0.3481	2.07	0.7206	**0.5307**	**1.9719**

			Standard Deviation (SD)	1.6694						
			d-1.96*SD	**-2.0207**	√(3*s^2/n)	0.6029	2.07	1.2480	-3.2688	-0.7727
			d+1.96*SD	**4.5233**	√(3*s^2/n)	0.6029	2.07	1.2480	3.2753	5.7714

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Appendix B

Part B.1 – *Inverse Kinematics for Gait and Step-Up-and-Over during the stance phase*

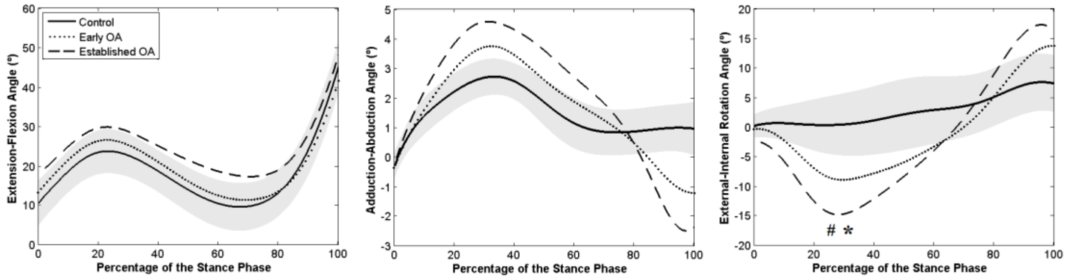

Figure B. 1– Averaged knee rotations in the sagittal, frontal and transversal planes during gait throughout the stance phase. The gray shaded area corresponds to the standard deviation of the control group. * indicates a significant difference between established OA and control group. # indicates a significant difference between early OA and control group.

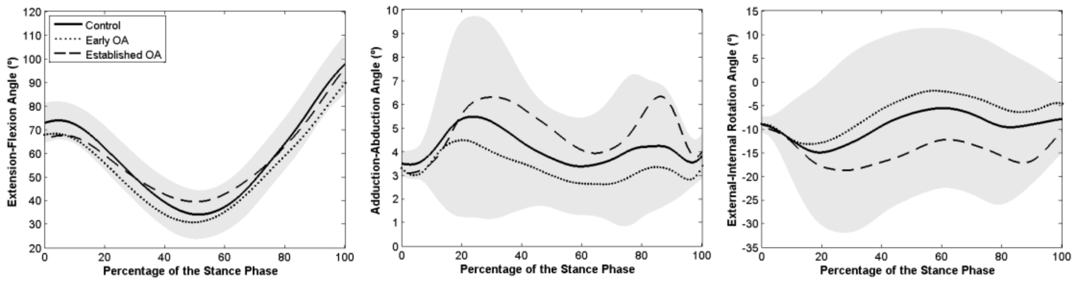

Figure B. 2 - Averaged knee rotations in the sagittal, frontal and transversal planes during step-up-and-over throughout the stance phase. The gray shaded area corresponds to the standard deviation of the control group.

Part B.2 – *Maximum and minimum values for KCF and moments*

Table B. 1 - Peak and SS values of the KCF, KFM, KAM and KRM during the stance phase of gait for control (C0), early OA (EA) and established OA (ES) groups, and rotation angles (RAngle in degrees), maximum contact pressures (MCP in MPa) and the location of the CoP (AP and LM in mm) relative to the tibia reference frame at the articular surface of the tibia plateau at the time instant of the first peak MKCF.

Total (80)		Control (34 legs)	Early OA (21 legs)	Established OA (25 legs)	*p*	*p* (C0 vs EA)	*p* (C0 vs ES)	*p* (EA vs ES)	*f*
P1	KFM	0.043±0.017	0.050±0.019	0.048±0.021	0.392	0.487	0.694	0.983	0.16
	KAM	0.026±0.005	0.026±0.010	0.028±0.008	0.614	0.964	0.885	0.699	0.12
	KRM	0.003±0.003	0.015±0.013	0.015±0.014	**0.001***	**0.000**	**0.000**	1.000	**0.57**
	TKCF	3.16±0.74	3.77±0.95	3.91±1.23	**0.008***	0.073	**0.012**	0.941	**0.35**
	MKCF	2.17±0.40	2.61±0.67	2.84±0.89	**0.001***	**0.048**	**0.001**	0.549	**0.45**
	LKCF	1.18±0.41	1.40±0.49	1.28±0.56	0.265	0.275	0.841	0.760	0.18
P2	KFM	0.026±0.011	0.026±0.008	0.030±0.013	0.277	0.989	0.449	0.380	0.17
	KRM	-0.005±0.003	-0.010±0.012	-0.012±0.016	**0.047**	0.360	**0.046**	0.805	0.28
	TKCF	2.84±0.39	3.12±0.40	3.28±0.82	**0.014**	0.199	**0.013**	0.748	**0.34**
	MKCF	1.80±0.30	1.89±0.46	2.06±0.55	0.084	0.869	0.078	0.437	0.26
	LKCF	1.21±0.27	1.48±0.48	1.56±0.57	**0.007**	0.086	**0.009**	0.880	**0.36**
SS	KFM	-0.007±0.013	-0.005±0.014	0.007±0.017	**0.001**	0.984	**0.002**	**0.014**	**0.42**
	TKCF	1.43±0.20	1.58±0.35	1.83±0.50	**0.000**	0.347	**0.000**	0.053	**0.48**
	MKCF	1.12±0.18	1.20±0.28	1.40±0.36	**0.001**	0.665	**0.000**	**0.033**	**0.44**
	LKCF	0.32±0.13	0.36±0.25	0.37±0.26	0.570	0.844	0.679	0.996	0.11
RAngle		0.30±5.10	-7.45±14.00	-14.61±14.28	**0.000**	**0.042**	**0.000**	0.098	**0.71**
MCP Tibia		15.02±3.44	19.72±8.12	25.78±10.82	**0.000**	0.083	**0.000**	**0.027**	**0.60**
AP		-2.20±2.07	-3.63±2.08	-4.07±1.69	**0.001**	**0.029**	**0.002**	0.832	-
LM		-21.17±0.58	-21.22±1.17	-20.27±1.28	**0.001**	0.998	**0.003**	**0.006**	-

Statistically significances ($p < 0.05$) are indicated in bold and calculated by *post-hoc* Gabriel calculated by ANOVA. KFM, KAM and KRM are expressed as mean ± SD (BW*Ht), and KCF as (mean ± SD (BW)), where SD is standard deviation. P1 and P2 correspond, respectively, to first and second peak and SS to the minimum value during the single support phase.
Positive values of RAngle indicate internal rotation and negative values indicate external rotation.
AP – Anterior-Posterior direction, in which negative values correspond to a more posterior region and positive to a more anterior region; LM – Lateral-Medial direction, in which negative values correspond to a more medial region and positive to a more lateral region.

Table B. 2 - Peak and SS values of the KCF, KFM and KAM during the stance phase of step-up-and-over for control (C0), early OA (EA) and established OA (ES) groups.

		Control (37 legs)	**Early OA (25 legs)**	**Established OA (24 legs)**	***p***	***p* (C0 vs EA)**	***p* (C0 vs ES)**	***p* (EA vs ES)**	***f***
P1	**KFM**	0.077±0.025	0.077±0.022	0.062±0.022	**0.025***	1.000	**0.038**	0.060	0.29
	KAM	0.025±0.010	0.022±0.010	0.022±0.009	0.332	0.443	0.589	0.997	0.15
	TKCF	4.94±1.57	4.94±1.54	4.49±1.47	0.467	1.000	0.588	0.654	0.13
	LKCF	2.50±1.32	2.63±1.25	2.38±1.91	0.776	0.967	0.977	0.856	0.06
P2	**KFM**	0.101±0.022	0.101±0.024	0.092±0.019	0.214	1.000	0.278	0.373	0.19
	KAM	0.023±0.009	0.020±0.007	0.022±0.010	0.293	0.309	0.877	0.794	0.14
	TKCF	5.64±1.10	5.65±1.35	5.88±1.29	0.719	1.000	0.835	0.873	0.08
	LKCF	2.93±1.00	3.08±1.13	3.50±1.21	0.139	0.935	0.139	0.442	0.21
SS	**KFM**	0.028±0.020	0.029±0.023	0.034±0.024	0.609	0.999	0.707	0.832	0.12
	KAM	0.013±0.007	0.010±0.008	0.012±0.008	0.218	0.229	0.730	0.842	0.16
	TKCF	2.55±1.18	2.47±1.07	3.11±1.26	0.102	0.990	0.186	0.151	0.23
	LKCF	0.83±0.59	0.86±0.59	1.11±0.73	0.198	0.998	0.239	0.392	0.19
Highest MKCF		3.16±0.53	3.20±0.66	3.03±0.79	0.589	0.989	0.809	0.691	0.10

Statistically significances ($p < 0.05$) are indicated in bold and calculated by *post-hoc* Gabriel calculated by ANOVA. KFM, KAM and KRM are expressed as mean ± SD (BW*Ht), and KCF as (mean ± SD (BW)), where SD is standard deviation. P1 and P2 correspond, respectively, to first and second peak and SS to the minimum value during the single support phase.

Appendix C

Part C.1 - Contact Forces

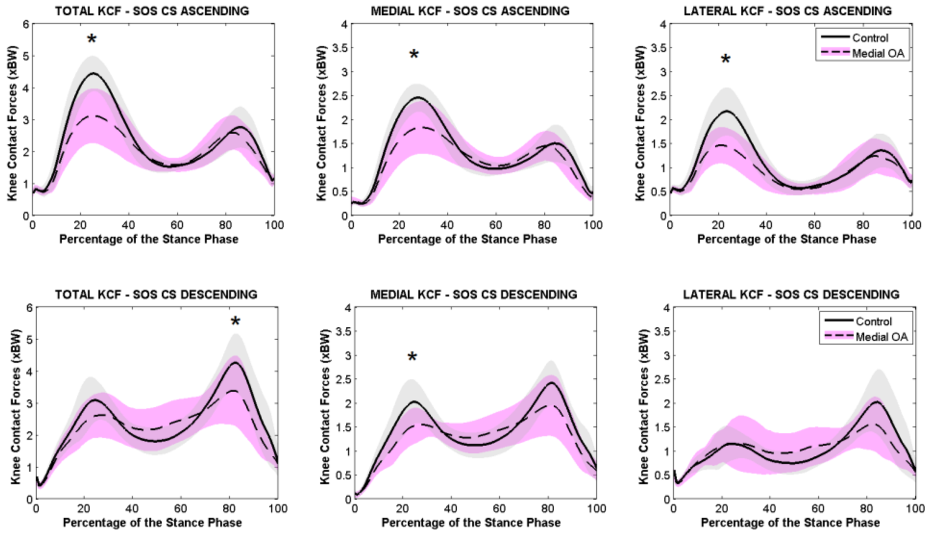

Figure C. 1 - Total, medial and lateral knee contact forces (KCF) during step-over-step (SOS) at controlled speed while ascending (above) and descending stairs (below) comparing healthy subjects and individuals with medial knee OA. * indicates a significant difference between the groups.

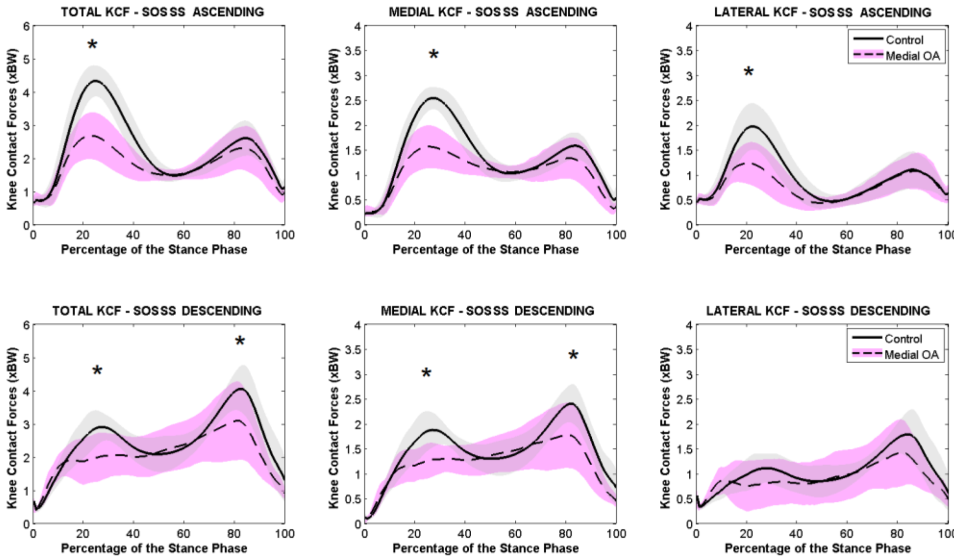

Figure C. 2 - Total, medial and lateral knee contact forces (KCF) during step-over-step (SOS) at self-selected speed while ascending (above) and descending stairs (below) comparing healthy subjects and individuals with medial knee OA. * indicates a significant difference between the groups.

Table C. 1 - Peak values of the total, medial and lateral KCF (×BW) during the stance phase of step-over-step at self-selected speed (SOS SS), step-over-step at controlled speed (SOS CS) and step-by-step (SBS) while ascending (ASC) and descending (DESC) stairs comparing between the control (C0) group and the medial OA (OA) group.

			Total (26)	Control (16 legs)	Medial OA (10 legs)	*P* (C0 vs OA)
SOS CS	ASC	P1	TKCF	4.49 (0.85)	3.17 (0.82)	**0.001**
			MKCF	2.51 (0.28)	1.86 (0.54)	**0.000**
			LKCF	2.24 (0.81)	1.52 (0.36)	**0.015**
		P2	TKCF	2.82 (0.65)	2.65 (0.53)	0.492
			MKCF	1.56 (0.62)	1.52 (0.35)	0.868
			LKCF	1.39 (0.43)	1.26 (0.44)	0.454
	DESC	P1	TKCF	3.26 (0.81)	2.72 (0.75)	0.104
			MKCF	2.11 (0.57)	1.58 (0.41)	**0.019**
			LKCF	1.28 (0.36)	1.34 (0.42)	0.682
		P2	TKCF	4.33 (0.96)	3.43 (1.12)	**0.038**
			MKCF	2.44 (0.54)	1.98 (0.65)	0.063
			LKCF	2.11 (0.72)	1.58 (0.58)	0.062
SOS SS	ASC	P1	TKCF	4.41 (0.78)	2.78 (0.62)	**0.000**
			MKCF	2.61 (0.26)	1.64 (0.45)	**0.000**
			LKCF	2.04 (0.67)	1.32 (0.29)	**0.004**
		P2	TKCF	2.64 (0.53)	2.42 (0.68)	0.354
			MKCF	1.61 (0.49)	1.40 (0.53)	0.318
			LKCF	1.14 (0.42)	1.13 (0.38)	0.967
	DESC	P1	TKCF	3.13 (0.64)	2.34 (0.58)	**0.004**
			MKCF	2.01 (0.44)	1.40 (0.31)	**0.001**
			LKCF	1.28 (0.31)	1.18 (0.38)	0.478
		P2	TKCF	4.20 (0.74)	3.29 (1.14)	**0.021**
			MKCF	2.44 (0.43)	1.90 (0.58)	**0.011**
			LKCF	1.92 (0.53)	1.52 (0.72)	0.115

SBS	**ASC**	**P1**	**TKCF**	4.56 (0.86)	2.94 (0.70)	**<u>0.000</u>**
			MKCF	2.64 (0.34)	1.81 (0.40)	**<u>0.000</u>**
			LKCF	2.17 (0.69)	1.36 (0.31)	**<u>0.002</u>**
	DESC	**P1**	**TKCF**	4.44 (0.73)	3.48 (1.03)	**<u>0.010</u>**
			MKCF	2.43 (0.35)	1.95 (0.50)	**<u>0.009</u>**
			LKCF	2.31 (0.60)	1.73 (0.74)	**<u>0.037</u>**

Statistically significant differences ($P < 0.05$) are indicated in bold and calculated by paired-samples *t*-test. KCF are expressed as mean (SD (BW), where SD is standard deviation. P1 and P2 correspond, respectively, to first and second peak of the stance phase.

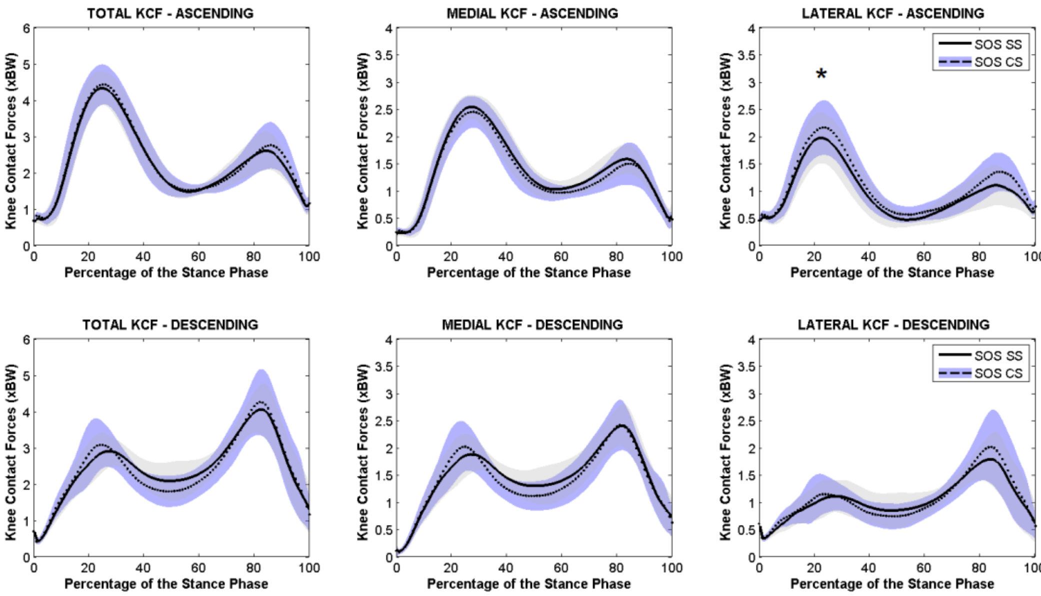

Figure C. 3 - Total, medial and lateral knee contact forces (KCF) in healthy subjects comparing step-over-step at self-selected speed (SOS SS) and step-over-step at controlled speed (SOS CS) while ascending (above) and descending (below) stairs. * indicates a significant difference between the two tasks.

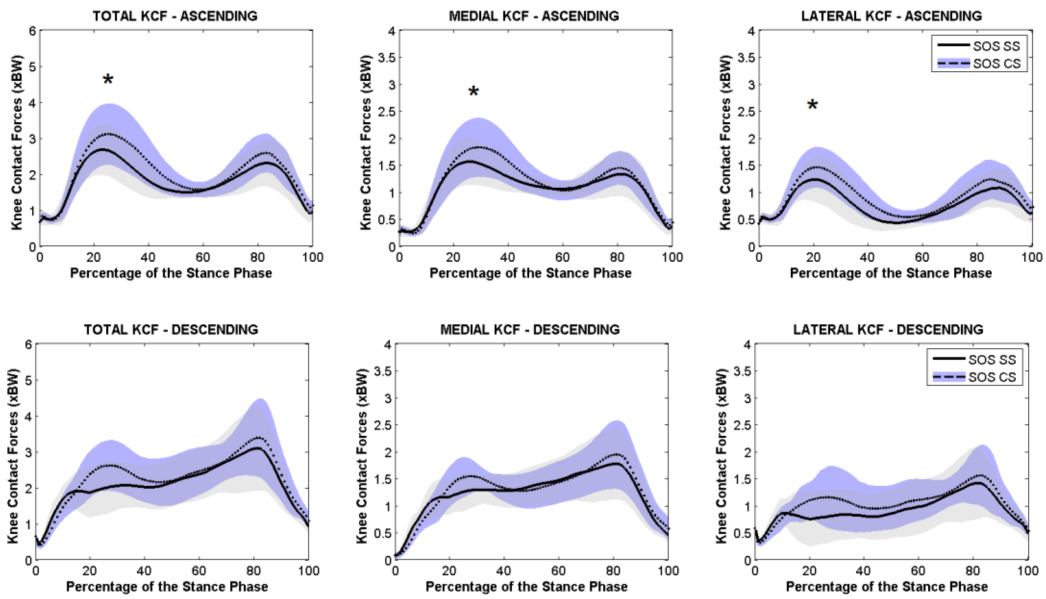

Figure C. 4 - Total, medial and lateral knee contact forces (KCF) in individuals with medial knee OA comparing step-over-step at self-selected speed (SOS SS) and step-over-step at controlled speed (SOS CS) while ascending (above) and descending (below) stairs. * indicates a significant difference between the two tasks.

Table C. 2 - Peak values of the total, medial and lateral KCF (×BW) during the stance phase of step-over-step at self-selected speed (SOS SS), step-over-step at controlled speed (SOS CS) and step-by-step (SBS) while ascending (ASC) and descending (DESC) stairs for the control and medial OA groups comparing between tasks.

		ASCENDING (ASC)					DESCENDING (DESC)				
		SOS CS	SOS SS	SBS	*P* CS *vs* SS)	*P* (SS *vs* SBS)	SOS CS	SOS SS	SBS	*P* (CS *vs* SS)	*P* (SS *vs* SBS)
CONTROL	TKCF	4.49 (0.85)	4.41 (0.78)	4.56 (0.86)	0.414	0.182	4.33 (0.96)	4.20 (0.74)	4.44 (0.73)	0.473	0.087
	MKCF	2.51 (0.28)	2.61 (0.26)	2.64 (0.34)	0.190	0.672	2.44 (0.54)	2.44 (0.43)	2.43 (0.35)	0.977	0.797
	LKCF	2.24 (0.81)	2.04 (0.67)	2.17 (0.69)	**0.009**	0.066	2.11 (0.72)	1.92 (0.53)	2.31 (0.60)	0.144	**0.016**
MEDIAL OA	TKCF	3.17 (0.82)	2.78 (0.62)	2.94 (0.70)	**0.007**	0.101	3.43 (1.12)	3.29 (1.14)	3.48 (1.03)	0.506	0.215
	MKCF	1.86 (0.54)	1.64 (0.45)	1.81 (0.40)	**0.024**	**0.008**	1.98 (0.65)	1.90 (0.58)	1.95 (0.50)	0.547	0.657
	LKCF	1.52 (0.36)	1.32 (0.29)	1.36 (0.31)	**0.002**	0.425	1.58 (0.58)	1.52 (0.72)	1.73 (0.74)	0.628	**0.040**

Statistically significant differences ($P < 0.05$) are indicated in bold and calculated by independent-samples *t*-test. KCF are expressed as mean (SD (BW), where SD is standard deviation. KCF corresponding to the peak KCF of the different tasks, i.e., first and second peak KCFs for ascending and descending, respectively.

Part C.2 – Centre of Pressures

Table C. 3 - Centre of pressure (CoP, mm) comparing the two groups of subjects.

			Control (16 legs)	Medial OA (10 legs)	*P* (C0 vs OA)
SOS CS	**ASC**	**CoP (PA)**	-4.8 (1.2)	-4.2 (2.4)	*0.399*
		CoP (ML)	-20.5 (1.5)	-21.9 (1.1)	***0.019***
	DESC	**CoP (PA)**	-3.3 (1.3)	-2.3 (1.3)	*0.057*
		CoP (ML)	-21.1 (1.6)	-22.0 (1.3)	*0.157*
SOS SS	**ASC**	**CoP (PA)**	-5.2 (1.4)	-3.5 (2.2)	***0.025***
		CoP (ML)	-21.0 (1.7)	-21.5 (1.1)	*0.400*
	DESC	**CoP (PA)**	-3.4 (1.11)	-2.1 (1.7)	***0.021***
		CoP (ML)	-21.5 (1.38)	-22.2 (1.2)	*0.177*
SBS	**ASC**	**CoP (PA)**	-5.2 (0.8)	-4.4 (1.9)	*0.167*
		CoP (ML)	-20.9 (1.6)	-22.3 (1.4)	***0.036***
	DESC	**CoP (PA)**	-3.4 (0.8)	-3.0 (1.8)	*0.510*
		CoP (ML)	-20.6 (1.5)	-22.0 (1.3)	***0.027***

Statistically significant differences (P < 0.05) in the centre of pressure (CoP) location between the two groups of subjects, evaluated by the independent *t*-test, are indicated in bold.
PA – Posterior-Anterior direction, in which negative values correspond to a more posterior region and positive to a more anterior region; ML – Medial-Lateral direction, in which negative values correspond to a more medial region and positive to a more lateral region.

Table C. 4 - p- values for the centre of pressure (CoP) comparing activities into the groups.

		ASCENDING (Asc)		DESCENDING (Desc)	
		SOS CS vs SOS SS	**SOS SS vs SBS**	**SOS CS vs SOS SS**	**SOS SS vs SBS**
Control (16 legs)	**CoP (AP)**	*0.155*	*0.974*	*0.679*	*0.705*
	CoP (LM)	***0.000***	*0.265*	***0.033***	***0.000***
Medial OA (10 legs)	**CoP (AP)**	*0.144*	***0.005***	*0.640*	***0.019***
	CoP (LM)	***0.034***	***0.011***	*0.415*	*0.220*

Statistically significant differences (P < 0.05) in the CoP location between strategies within each group of subjects, evaluated by the paired-sample *t*-test, are indicated in bold.

Part C.3 - Kinetics

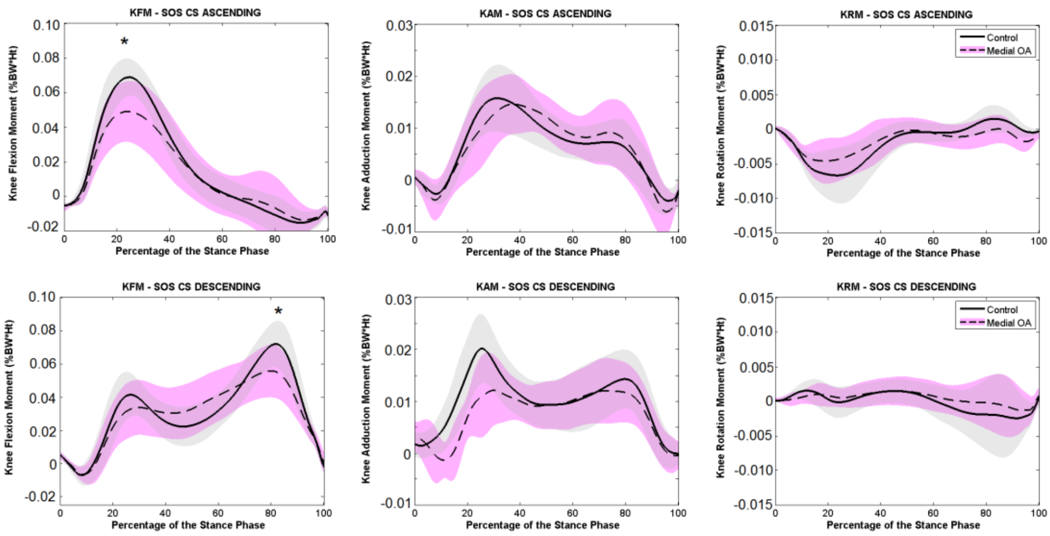

Figure C. 5 - Knee flexion (left), adduction (middle) and rotation (right) moments during step-over-step (SOS) at controlled speed while ascending (above) and descending stairs (below) comparing healthy subjects and individuals with medial knee OA. * indicates a significant difference between the groups.

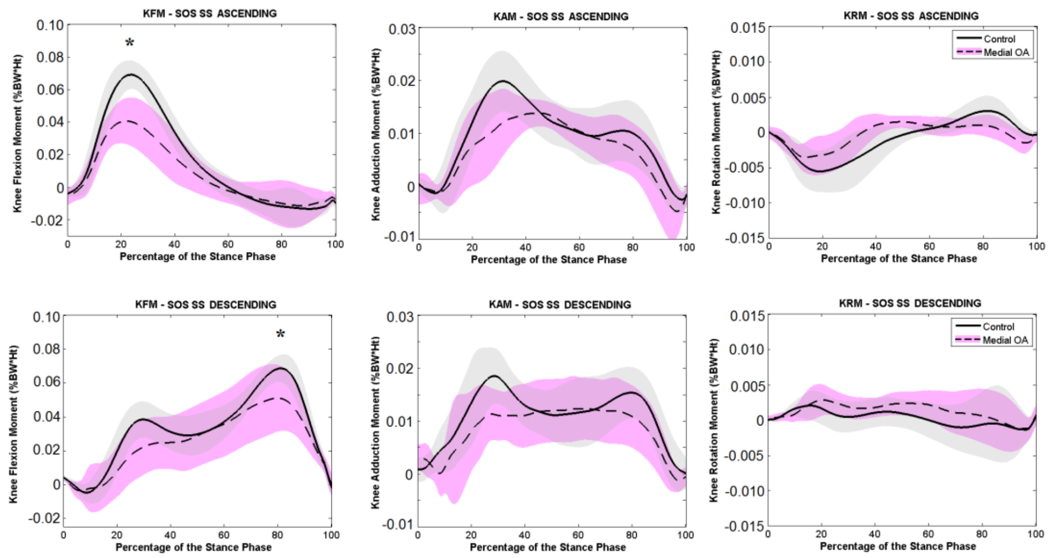

Figure C. 6 - Knee flexion (left), adduction (middle) and rotation (right) moments during step-over-step (SOS) at self-selected speed while ascending (above) and descending stairs (below) comparing healthy subjects and individuals with medial knee OA. * indicates a significant difference between the groups.

Table C. 5 – Peak values of the KFM, KAM and KRM (BW*Ht) during stance phase of step-over-step at self-selected speed (SOS SS), step-over-step at controlled speed (SOS CS) and step-by-step (SBS) while ascending (ASC) and descending stairs (DESC).

				Total (26)	**Control (16 legs)**	**Medial OA (10 legs)**	***P* (C0 vs OA)**
SOS CS	**ASC**	**P1**	**KAM**	0.017 (0.009)	0.016 (0.008)	0.805	
			KFM	0.070 (0.012)	0.050 (0.017)	**0.002**	
			KRM	-0.008 (0.006)	-0.006 (0.004)	0.235	
		P2	**KRM**	0.002 (0.003)	0.001 (0.003)	0.633	
	DESC	**P2**	**KAM**	0.021 (0.008)	0.016 (0.007)	0.119	
			KFM	0.073 (0.015)	0.058 (0.018)	**0.022**	
SOS SS	**ASC**	**P1**	**KAM**	0.021 (0.010)	0.016 (0.006)	0.141	
			KFM	0.071 (0.010)	0.043 (0.013)	**0.000**	
			KRM	-0.007 (0.006)	-0.004 (0.003)	0.184	
		P2	**KRM**	0.003 (0.003)	0.003 (0.002)	0.464	
	DESC	**P2**	**KAM**	0.021 (0.007)	0.016 (0.006)	0.071	
			KFM	0.070 (0.009)	0.054 (0.020)	**0.010**	
SBS	**ASC**	**P1**	**KAM**	0.018 (0.008)	0.016 (0.007)	0.549	
			KFM	0.072 (0.011)	0.046 (0.013)	**0.000**	
	DESC	**P2**	**KAM**	0.015 (0.004)	0.014 (0.004)	0.698	
			KFM	0.073 (0.010)	0.054 (0.017)	**0.001**	

Statistically significant differences ($P < 0.05$) are indicated in bold and calculated by paired-samples *t*-test. Knee moments are expressed as mean (SD (BW*Ht), where SD is standard deviation. P1 and P2 correspond, respectively, to first and second peak of the stance phase.

Part C.4 - Kinematics

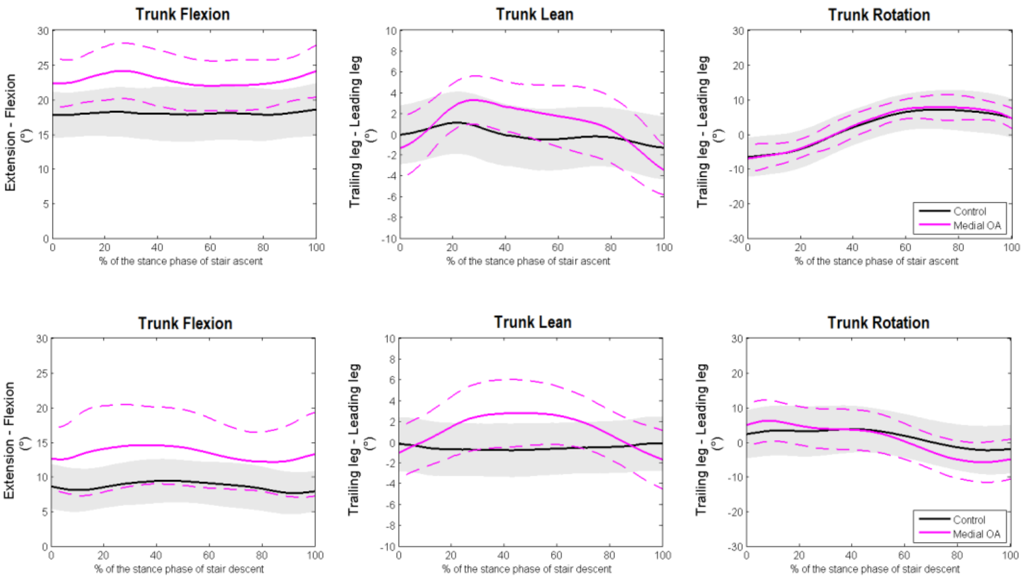

Figure C. 7 - Trunk kinematics relative to the ground reference frame in the sagittal (left), frontal (middle) and transversal (right) plane for step-over-step (SOS) while ascending (above) and descending (below) stairs at self-selected speed during stance phase, comparing healthy subjects and individuals with medial knee OA.

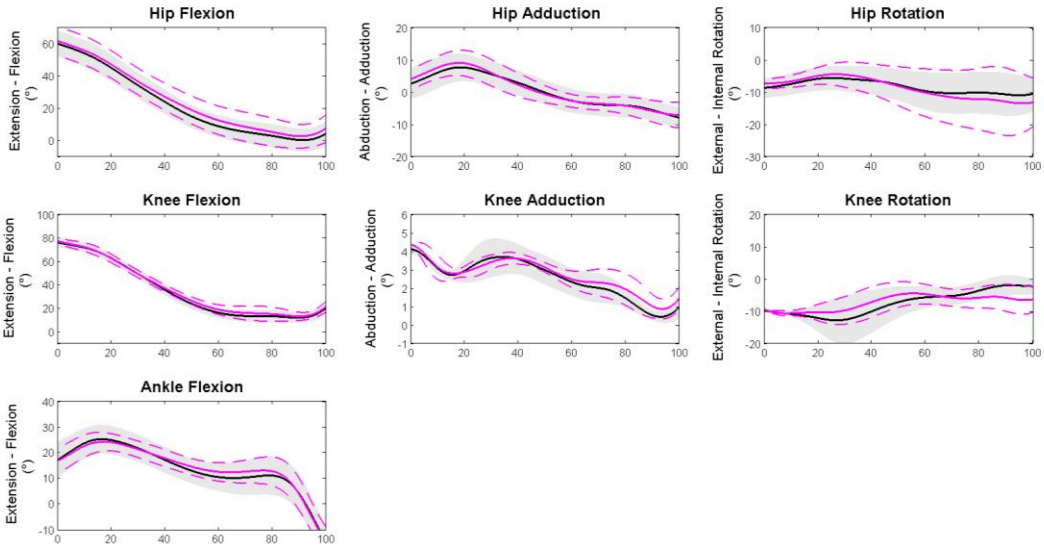

Figure C. 8 - Hip, knee and ankle kinematics at the sagittal (left), frontal (middle) and transversal (right) planes of rotation for step-over-step (SOS) while ascending stairs at controlled speed during stance phase comparing healthy subjects and individuals with medial knee OA.

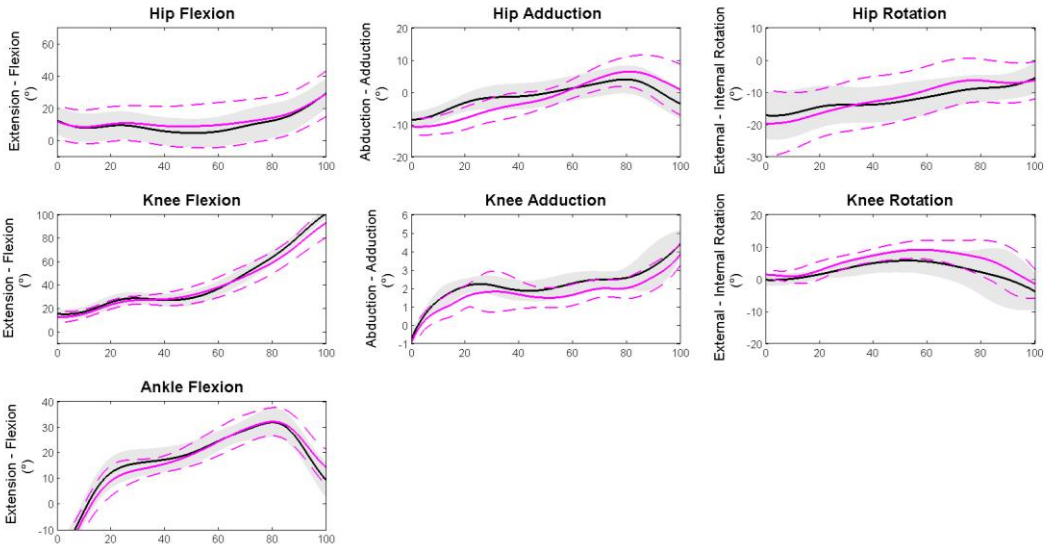

Figure C. 9 - Hip, knee and ankle kinematics at the sagittal (left), frontal (middle) and transversal (right) planes of rotation for step-over-step (SOS) while descending stairs at controlled speed during stance phase comparing subjects and individuals with medial knee OA.

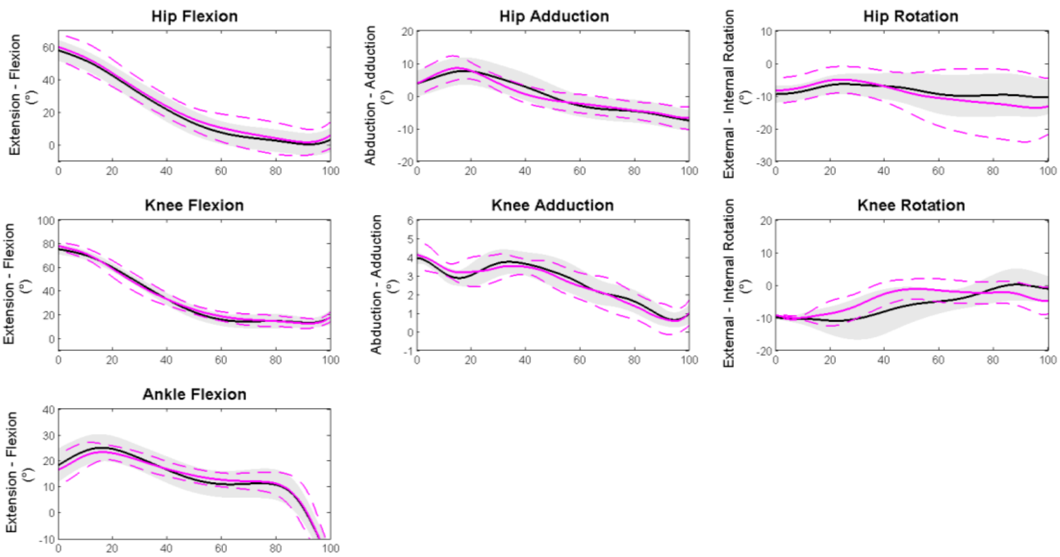

Figure C. 10 - Hip, knee and ankle kinematics at the sagittal (left), frontal (middle) and transversal (right) planes of rotation for step-over-step (SOS) while ascending stairs at self-selected speed during stance phase comparing healthy subjects and individuals with medial knee OA.

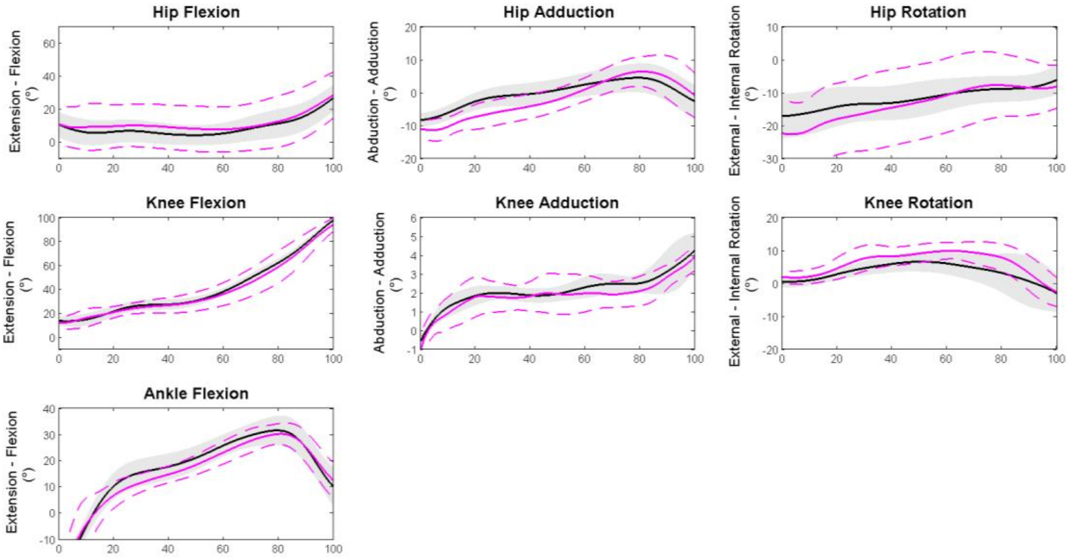

Figure C. 11 - Hip, knee and ankle kinematics at the sagittal (left), frontal (middle) and transversal (right) planes of rotation for step-over-step (SOS) while descending stairs at self-selected speed during stance phase comparing healthy subjects and individuals with medial knee OA.

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Acknowledgements

I want to dedicate the first paragraph to the amazing supervisor team that I have been working with for the last four years: Ilse Jonkers, Neil Reeves, Friedl De Groote and Sabine Verschueren. I would like to start by expressing my deepest gratitude to my supervisor Ilse Jonkers, to whom I owe for her inspiration, knowledge and expertise, dedication and encouragement, but also her patience. Ilse was a central figure in helping me settle down in Leuven and introducing me to this research topic. The uncountable meetings and brainstorming sessions I had the chance to be part of together with Jonkers, De Groote, Reeves and Verschueren were essential for the success of this project but also for my own professional progression. A large thanks to Friedl, to whom I owe for her impressive knowledge and expertise, kindness and availability. A great thanks to Neil for taking over the role of my supervisor after Costis Maganaris left, for sharing your expertise with me and for being so supportive and available. Neil has worked closely with me during all my experiments performed at MMU, making part of the work not only as a supervisor but also as an indispensable collaborator in the lab with my participants. A large thanks to Sabine for being so available in helping me and for her knowledge and expertise contribution to this project. A great thank to Dr. Richard Jones, who, although was not my supervisor, supported my work performed in Manchester with an incredible passion and dedication to this topic. Thank you also for your expertise and collaboration.

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About the author

Biography

Susana Patrícia Ferreira Meireles was born on March 10th, 1982 in Porto, Portugal. Susana completed her bachelor's and master's degree in Biomedical Engineering in 2008 at the Universidade do Minho in Braga, and Universidade de Aveiro in Aveiro, Portugal, where she conducted her master's project. After graduation, she was offered to work as a researcher in the Department of Mechanical Engineering at the Universidade de Aveiro, where she developed a 3D finite element model of the radiocarpal joint and performed FE analysis of a total wrist prosthesis. In the same context she moved to Rochester, Minnesota, USA for 4 months to conduct some experimental tests at the Biomechanics and Motion Analysis Lab at Mayo Clinic under the supervision of Dr. Kai-Nan An. In 2012, she started working at the IDMEC – Faculdade de Engenharia Mecânica da Universidade do Porto, under supervision of Prof. Renato Natal, where she performed biomechanical studies on the inner ear. After this academic experience, she moved to the private sector to work as a programmer at Accenture in Lisboa, Portugal. A few months later, she received European Commision PhD fellowship through Move Age, an Erasmus Joint Doctorate Programme for pursuing doctoral research at the Department of Kinesiology, KU Leuven in Belgium under supervision of Prof. Ilse Jonkers and Manchester Metropolitan University, United Kingdom under supervision of Prof Neil Reeves.

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